Sickle Cell Anemia Patients Have Low Erythropoietin Levels for Their Degree of Anemia

By Judith B. Sherwood, Eugene Goldwasser, Robert Chilcote, L. David Carmichael, and Ronald L. Nagel

We have studied serum immunoreactive erythropoietin (SIE) levels in 28 patients with sickle cell anemia (SCA) without renal insufficiency and in 17 patients with nonhemoglobinopathy anemias of comparable severity using a sensitive radioimmunoassay procedure. An exponential relationship between SIE level and degree of anemia was noted in all patients. However, in nonhemoglobinopathy anemia, a sharp rise in the SIE level occurred as hemoglobin (Hb) levels fell below about 12 g/dL, whereas in sickle cell patients the increase was not marked until hemoglobin fell to about 9 g/dL. The response was more blunted in older SCA patients than in younger ones. A linear regression model relating SIE level to Hb level, presence/absence of SCA, and age explained 63% of the variation in SIE. We conclude that the serum erythropoietin levels in SCA increased at a lower hemoglobin concentration and are of a lower magnitude than that of the other anemias.

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ERYTHROPOIETIN IN SICKLE CELL ANEMIA

### Table 1. Laboratory Values of Anemic Patients

<table>
<thead>
<tr>
<th>Anemia</th>
<th>No. of Patients</th>
<th>Hb (g/dL)</th>
<th>Hct (%)</th>
<th>Retic (%)</th>
<th>Hbf (%)</th>
<th>MCV (µm³)</th>
<th>MCH (pg)</th>
<th>MCHC (%)</th>
<th>Bilirubin (mg/dL)</th>
<th>EPO (mU/mL, serum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle Cell Anemia</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>9.2 ± 5.5 yr (1-17)</td>
<td>18</td>
<td>7.61 ± 1.58</td>
<td>21.4 ± 4.71</td>
<td>19.35 ± 10.1</td>
<td>6.49 ± 6.8</td>
<td>90.17 ± 10.5</td>
<td>32.95 ± 5.5</td>
<td>36.25 ± 2.8</td>
<td>1.97 ± 2.8</td>
<td>192.52 ± 291.7</td>
</tr>
<tr>
<td>31 ± 6.6 yr (22-40)</td>
<td>10</td>
<td>8.08 ± 1.46</td>
<td>14.1 ± 2.9</td>
<td>10.3 ± 4.4</td>
<td>5.2 ± 3.2</td>
<td>95.8 ± 9.6</td>
<td>32.9 ± 2.5</td>
<td>34.3 ± 2.2</td>
<td>3.2 ± 1.6</td>
<td>56 ± 63</td>
</tr>
<tr>
<td>Nonhemolytic</td>
<td>13</td>
<td>9.9 ± ± 7</td>
<td>28.5 ± 19.1</td>
<td>—</td>
<td>934 ± 19.1</td>
<td>32.3 ± 6.6</td>
<td>34.6 ± 1.9</td>
<td>2 ± 3.5</td>
<td>420 ± 366</td>
<td></td>
</tr>
<tr>
<td>Nonhemoglobinopathy</td>
<td>4</td>
<td>8.88 ± 3.92</td>
<td>26.40 ± 1.14</td>
<td>32.17 ± 30.3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>395.0 ± 195.0</td>
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<td>Hemolytic, Nonhemoglobinopathy</td>
<td>4</td>
<td>8.88 ± 3.92</td>
<td>26.40 ± 1.14</td>
<td>32.17 ± 30.3</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>395.0 ± 195.0</td>
</tr>
</tbody>
</table>

Abbreviations: Hct, hematocrit; EPO, erythropoietin; Hb, hemoglobin.

Values are expressed as mean ± SD. Numbers in parentheses are the range of values. Hematologic indexes (MCV, MCH, MCHC) were obtained by the Coulter Counter (Coulter Electronics, Hialeah, Fla). Erythropoietin values were determined in the radioimmunoassay.

### RESULTS

SIE levels were measured in 17 patients with anemias of various causes not associated with sickle cell anemia, other hemoglobinopathies, or renal disease (including four patients with hemolytic anemia) and in 28 patients with sickle cell anemia (ten adults and 18 children); of these, the 17 non-sickle cell anemia patients and 26 sickle cell anemia patients for whom all variables were recorded were used in the analysis. The two patients with Sδ-thal that were analyzed separately. We found that Hb level, age, and sickle cell anemia status predicted 63% (R²) of the variance in SIE (Figs 1 and 2), with F = 22.0 (P < 2 × 10⁻⁴). The significance of the contribution of the individual terms was tested, and presence/absence of sickle cell anemia was highly significant (P < .0004); the effect of age, however, was significant only among sickle cell anemia patients (P = .011).

The adult sickle cell anemia patient with 220 mU/mL of SIE appeared to be an outlier; however, there were no major alterations in the model when this patient was excluded, and there appeared to be no technical reasons to question the accuracy of the SIE determination.

The mean SIE level of the anemic patients was significantly higher than the normal value of 21 ± 6 (± SD) mU/mL previously found with this radioimmunoassay. The 17 patients with nonhemoglobinopathy-associated anemias had the highest levels: 414 ± 327 mU/mL of serum (range, 21 to 1,300 mU/mL), with a mean hemoglobin concentration of 9.7 ± 2.5 g/dL (range, 6.1 to 12.8 g/dL). The mean SIE level of the four patients with hemolytic anemias not associated with hemoglobinopathy was 395 ± 195 mU/mL (range, 220 to 610 mU/mL), a value that did not differ significantly from the levels found in the other nonhemoglobinopathy anemias (Fig 1). The mean value found for the patients with sickle cell anemia was 144 ± 234 mU/mL of serum (range 12 to 1,300 mU/mL), with a mean hemoglobin concentration of 7.8 ± 1.5 g/dL (range, 3 to 11 g/dL). As shown in Fig 2, the sickle cell anemia patients have less SIE at any level of hemoglobin; SIE levels rise only when considerably lower Hb levels are reached, as compared with non-sickle cell anemia patients.

The adult sickle cell anemia patients had a mean SIE level of 56 ± 63 mU/mL of serum (range, 12 to 220 mU/mL)

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**Fig 1.** Erythropoietin levels in nonhemoglobinopathy anemias for 13 patients with nonhemolytic (△) and four patients with autoimmune hemolytic (○) anemia. The line represents the regression equation log (SIE = 10) = 8.91 - 0.35 (Hb), and the crosshatched box indicates the normal range.

**Fig 2.** Erythropoietin levels in sickle cell anemia for 18 pediatric (Δ) and ten adult (△) patients: two children with Sδ-thal disease (○) are also shown. The regression equation log (SIE = 10) = 8.91 - 0.64 (Hb) - 0.04 (age) is shown for the mean age of the two age groups.
with a mean hemoglobin concentration of 8.1 ± 1.5 g/dL (range, 6 to 11 g/dL). The children with sickle cell anemia, with a similar hemoglobin concentration of 7.6 ± 1.6 g/dL (range, 3 to 10 g/dL), had a mean SIE level of 193 ± 292 mU/mL of serum (range, 27 to 1,300 mU/mL). When a child with 3 g/dL hemoglobin and an erythropoietin level of 1,300 mU/mL was excluded, the mean SIE level for the children was 127 ± 96 mU/mL, and the mean hemoglobin level was 7.9 ± 1.1 g/dL. Analysis of covariance comparing the adult and pediatric sickle cell patients showed that the average erythropoietin level was significantly different at \( P < .02 \), even when the child with the very low hemoglobin level (3.1 g/dL) and high erythropoietin level (1,300 mU/mL) was not included in the computation.

The two children with Sb-thal had a mean Hb level of 7.6 ± 0.65 g/dL and an SIE level of 84.2 ± 33.8 mU/mL (50.5, 118). When they were included in the regression model, there was no significant alteration in its parameters, and its strength actually increased slightly (\( R^2 = 65\% \)).

DISCUSSION

SIE levels were determined in pediatric and adult patients with sickle cell disease and in patients with nonhemoglobinopathy anemias of various causes, including hemolytic anemias by using our sensitive radioimmunoassay procedure. An exponential relationship between the SIE level and the hemoglobin concentration was noted in all patients. In patients with nonhemoglobinopathy anemias, we observed a drastically increased slope at a hemoglobin concentration of approximately 11 g/dL or less (Figs 1 and 2). This hemoglobin level can be considered as a threshold. The data presented here on the inverse relationship between hemoglobin concentration and immunoreactive erythropoietin levels in anemias other than sickle cell (Fig 1) are in general agreement with the previously published data based on biologic activity.

The relationship between Hb levels and SIE in the sickle cell anemia patients departs from this since these patients exhibit elevated levels of erythropoietin only at a hemoglobin concentration below about 9 g/dL (Fig 2). The patients with nonhemoglobinopathy-associated anemias and other types of hemolytic anemias do not exhibit this hemoglobin threshold and have levels of SIE that are greater than that of the sickle cell patients (Fig 2). Our observation that patients with sickle cell anemia produce less immunoreactive erythropoietin at a given hemoglobin concentration than do patients with nonhemoglobinopathy anemias (hemolytic and nonhemolytic) agrees with a previous observation using the biologic assay.

We conclude that the relationship between SIE and Hb levels in sickle cell anemia can be described by an exponential curve that is significantly displaced to the left. In addition, the level of SIE reached by these patients is also significantly lower than that observed in other anemias. Analysis of the variables involved in the relationship between SIE and Hb levels by using a linear regression model indicated that age, Hb level, and presence or absence of anemia explained 63% (\( R^2 \)) of the variance in the SIE level. Of special interest is the effect of age, as pediatric sickle cell anemia patients tended to have significantly higher SIE levels than adults. The potential mechanism for the low SIE levels in sickle cell disease include interference with the renal synthesis of erythropoietin and the displacement to the right of the O2 equilibrium curve.

The well-known right shift in the oxygen equilibrium curve would facilitate oxygen delivery to the tissues, decreasing the hypoxic burden of a given level of anemia. Sickle cells have a higher p50 because of the intrinsically lower affinity for oxygen of the hemoglobin S polymer and because of the increase in intracellular 2,3-diphosphoglyceric acid levels. In addition, kinetic factors (decreased uptake and diffusion of \( O_2 \)) contribute to this anomaly in vivo.

Renal tissue damage in these patients might compromise the synthesis of erythropoietin or the hypoxia sensor presumed to be located in this organ. The renal damage, which differs from renal insufficiency, involves a concentration defect, progressive vascular damage particularly to the medulla, and structural abnormalities of the glomeruli and tubules. In favor of this interpretation is the age dependency of the level of SIE in sickle cell anemia patients (Fig 2). Individuals with chronic renal failure have SIE levels that are higher than normal, but lower than expected for the degree of anemia. In addition, Morgan et al observed that in adults with sickle cell anemia the concentration of erythropoietin was correlated positively with creatinine clearance and inversely with the BUN and that hemoglobin concentrations were depressed in the presence of minor degrees of renal insufficiency. Further work is necessary to establish definitively the mechanism of the decreased erythropoietin response in the patient with sickle cell anemia.

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REFERENCES


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