Two Cases of Familial Erythrocytosis With Increased Erythropoietin Activity in Plasma and Urine

By H. Yonemitsu, K. Yamaguchi, H. Shigeta, K. Okuda, and F. Takaku

Two brothers with familial erythrocytosis born to parents of a consanguinous marriage are described. Two other siblings were unaffected. There was a marked increase in erythropoietin concentration in both the plasma and urine, suggesting that a congenital defect led to erythropoietin-independent polycythemia. Other causes of polycythemia were excluded.

The first description of a familial erythrocytosis was in 1914, but it was not until 1933 that this condition was thoroughly reviewed and the name “benign familial polycythemia” was proposed by Sporado and Forskner. Only 19 families have been reported in the literature, including those found in Japan. Other proposed names include familial polycythemia, primary erythrocytosis, benign familial erythrocytosis, primary familial erythrocytosis, and familial erythrocytosis. Recently, Kontras and Romsho and Alperin et al. reported elevated erythropoietin activities in such patients. The present communication is concerned with the relationship of erythropoietin production to polycythemia in two cases of erythrocytosis occurring in siblings.

CASE REPORTS

Case I. K.O., a 19-yr-old boy, who had blood-shot eyes from childhood, was admitted to Chiba University Hospital on May 10, 1968 because of plethora. He was tall and thin, and had distinct flushing of the face and extremities. The blood pressure was 106/64, and the pulse rate was 72. The spleen was felt 2 cm below the left costal margin.

The hematologic studies are given in Table 1. Leukocyte alkaline phosphatase was low; the red cell mass measured with $^{51}$Cr was increased. He had a normal differential, moderate erythroid hyperplasia of the bone marrow, an erythrocyte sedimentation rate of 2 mm/hr, serum iron of 72 mg/100 ml, red cell half-life of 33 days, and normal osmotic fragility of the red cells. The bleeding and clotting times were normal.

Analysis of the hemoglobin revealed the following: Hb F 0.45%, Hb A$_2$ 2.7%, heat denaturation test 2.3%, solubility test 93%; an abnormal hemoglobin could not be detected on agar gel electrophoresis at pH 8.6 and 7.0. The oxygen affinity of Hb was normal. The total bilirubin was 1.63 mg of which 0.73 mg was direct bilirubin. The uric acid was 9.7 mg/100 ml. Renal function tests were normal. The basal metabolic rate was $+12^\circ$, the ACTH test was...
Table 1. Laboratory Values

<table>
<thead>
<tr>
<th></th>
<th>Father</th>
<th>Mother</th>
<th>Brother</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(60)</td>
<td>(47)</td>
<td>(23)</td>
<td>(19)</td>
<td>(19)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.8</td>
<td>11.0</td>
<td>14.7</td>
<td>22.4</td>
<td>22.4</td>
</tr>
<tr>
<td>RBC (per cu mm)</td>
<td>530 x 10⁴</td>
<td>382.5 x 10⁴</td>
<td>462 x 10⁴</td>
<td>1.032 x 10⁴</td>
<td>926 x 10⁴</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>45</td>
<td>38</td>
<td>46</td>
<td>81</td>
<td>72.5</td>
</tr>
<tr>
<td>WBC (per cu mm)</td>
<td>5,000</td>
<td>3,400</td>
<td>5,400</td>
<td>5,850</td>
<td>2,500</td>
</tr>
<tr>
<td>Reticulocyte (%)</td>
<td>0.7</td>
<td>0.2</td>
<td>0.2</td>
<td>0.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Platelet (per cu mm)</td>
<td>68,900</td>
<td>175,950</td>
<td>124,740</td>
<td>175,400</td>
<td>92,600</td>
</tr>
</tbody>
</table>

Neutrophile alkaline phosphatase

- Rate (%) 76, 94, 75, 55, 52
- Score * 247, 276, 197, 108, 118
- Total blood volume (ml/kg) — — — 110.0 107.7
- Total red cell volume (ml/kg) — — — 80.5 82.1

* Normal value 170-335 (mean 264)

normal, and the arterial oxygen saturation was 99%. Chromosomal analysis of a peripheral blood culture by the modified Moorhead method was normal. An EKG showed an incomplete right bundle branch block. Prominent vascular markings were seen in the chest x-ray, but the pulmonary functions were normal. Other roentgenologic studies including intravenous pyelography, upper gastrointestinal series, and the skull were within normal limits.

Case 2, No. 2, the younger brother of case 1, had a ruddy complexion from his childhood and entered the Chiba University Hospital on September 7, 1970, at the age of 19, with a complaint of recurrent headaches since the age of 15. Physical examination revealed a tall, thin male with flushed face and injected conjunctivae. The blood pressure was 95/55; the pulse was 76. The spleen was palpable 1 cm below the left costal margin, and there was a moderate enlargement of the thyroid.

The peripheral blood findings, red cell mass, total blood volume by ⁵¹Cr, and leukocyte alkaline phosphatase score are listed in Table 1. The peripheral blood differential was normal. There was moderate erythroid hyperplasia in the bone marrow. The erythrocyte sedimentation rate was 0 mm/hr; serum iron was 60 μg; unsaturated iron binding capacity was 361 μg/100 ml. Both direct and indirect Coombs tests were negative. The uric acid was 13.9 mg/100 ml. Renal function tests were normal. A thyroglobulin autorecognition test was negative; T₃ was 38", basal metabolic rate was 0~13", ¹³¹I uptakes were 33% (24 hr), the red cell half-life was 27 days. The hemoglobin studies were HbF 0.4", HbA₂ 2.7", heat denaturation tests 3.2", solubility test 91". There were no abnormal hemoglobins on agar gel electrophoresis (pH 8.6 and 7.0). The total bilirubin was 1.5 mg/100 ml, of which the direct bilirubin was 1.2 mg, but other liver function tests were within normal limits, and arterial oxygen saturation was 99%. The chromosome analysis on the peripheral blood culture was normal. Chest x-ray showed prominent pulmonary vascular markings, and the EKG showed an incomplete right bundle branch block. Intravenous pyelograms were normal. Electroencephalogram showed slow waves immediately after the occurrence of headache, but they returned to normal after 3 wk. Scanning with ¹³¹I revealed an enlarged thyroid and ¹²³I colloid visualized the bone marrow clearly.
FAMILIAL ERYTHROCYTOSIS

Exhypoxic polycythemia assay.

Patient 1. Patient 2.

Fig. 1. Pedigree of family: □, affected; ○, male and □, female (apparently unaffected or not investigated); †, deceased.

FAMILY STUDY

The parents of the patients had a consanguinous marriage (Fig. 1) and two of four siblings were affected. The hematologic studies of the parents and one other unaffected brother are also included in Table 1.

MEASUREMENT OF ERYTHROPOIETIN

Erythropoietin was measured by Takaku’s method in the plasma and urine of the patients. Both transfused and exhypoxic mice were employed for evaluation of case 1, and on the exhypoxic technique was used for case 2. The 24-hr urine was dialyzed and concentrated with carbowax, and subsequently lyophilized. The latter was dissolved in physiological saline and

Table 2. Plasma and Urine Erythropoietin Studies

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of mice</td>
<td>Specimen</td>
<td>$^{59}$Fe incorporation into RBC% (Mean ± SD)</td>
<td>Erythropoietin (U)</td>
<td>No of mice</td>
<td>Specimen</td>
</tr>
<tr>
<td>5</td>
<td>Plasma (ml/mouse)</td>
<td>131 ± 37 (215 ± 61)*</td>
<td>21</td>
<td>5</td>
<td>Plasma (ml/mouse)</td>
</tr>
<tr>
<td>4</td>
<td>Patient urine (1/4 of 24-hr urine)</td>
<td>152 ± 3.5</td>
<td>2.5</td>
<td>5</td>
<td>Patient urine (1/5 of 24-hr urine)</td>
</tr>
<tr>
<td>5</td>
<td>Normal urine (1/5 of 24-hr urine)</td>
<td>211 ± 0.45</td>
<td>0.4</td>
<td>5</td>
<td>Normal urine (1/5 of 24-hr urine)</td>
</tr>
<tr>
<td>5</td>
<td>Saline control</td>
<td>0.58 ± 0.23</td>
<td>0.4</td>
<td>5</td>
<td>Saline control</td>
</tr>
</tbody>
</table>

Polycythemic mouse assay (transfusion-polycythemia) | Polycythemic mouse assay (exhypoxic polycythemia)

* Exhypoxic polycythemia assay.
an aliquot was injected into four five mice. The 24-hr urine of normal persons was similarly treated and injected into five mice. The units of the erythropoietin were derived from a comparison with Standard B. There was a marked increase in erythropoietin activity in both the plasma and urine of the two patients (Table 2). The 24-hr urinary output of erythropoietin was 10 U in case 1 and 14 U in case 2, as compared with normal control values of 2 U in 24 hr.

**DISCUSSION**

A genetic basis has been suspected in the etiology of familial erythrocytosis, but only in about half the families previously described in the literature has the disease been traced to more than one generation. In others, the disease was seen in siblings. Both the recessive and dominant types of inheritance have been suggested, but controversy still exists. It is of interest, therefore, that the cases reported herein were the issue of a consanguinous marriage.

Although there has been considerable variation in the age at diagnosis of familial erythrocytosis, there are a number of instances in which plethora was noted at the time of birth or shortly thereafter. In our patients the diagnosis was made at age 19. The parents, however, had noted a ruddy complexion from infancy, which suggests an earlier onset. There was no indication of myeloid hyperplasia. The leukocyte alkaline phosphatase was low, as has been reported by Davey, and those of the unaffected family members were normal (Table 1). There were no abnormal chromosomes seen in our patients. In view of these findings and the absence of myelofibrosis, it seems unlikely that these patients had a myeloproliferative disease. There was no evidence to suggest any of those conditions associated with secondary erythrocytosis including abnormal hemoglobins. The latter is of importance in evaluation of patients with familial erythrocytosis. Among the previous reported cases of familial erythrocytosis, only Kontras and Romsh and Knock and Githens evaluated their patients for hemoglobinopathy. Thus, it is possible that some previously reported instances of familial erythrocytosis represented examples of abnormal hemoglobins. In the present cases both the total blood and red cell volumes were increased so that one could exclude stress erythrocytosis.

Abildgaard et al. were unable to demonstrate an increase in erythropoietin, although the technique in use at that time was relatively insensitive. Kontras and Romsh and Alperin et al., however, demonstrated increased levels of erythropoietin in patients with familial erythrocytosis and suggested that it had etiologic significance. In view of their results as well as ours and also in view of the fact that these patients frequently are affected from early infancy, it seems reasonable to suggest that the disease may result from an hereditary increase in erythropoietin production. The aberrant regulatory mechanism for erythropoietin production would then be genetically determined and as such the mechanism for erythrocytosis would differ from that of other types of familial erythrocytosis.

**ACKNOWLEDGMENT**

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REFERENCES

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