The Genetic Basis of Hereditary Elliptocytosis With Hemolysis

By Howard A. Pearson

Oval or elliptical shape of the circulating red cells is usually inherited as a benign morphologic anomaly. In the great majority of cases, hereditary elliptocytosis is not accompanied by other hematologic abnormalities, but a number of instances of severe hemolytic anemia associated with bizarre red cell changes including prominent elliptocytosis have been reported. Elliptocytosis is determined by an autosomal dominant gene which in many instances is transmitted as if linked to the Rh locus. The genetic makeup associated with the rare cases of hemolytic elliptocytosis is not clear. Although several instances of possible homozygosity have been reported, this is not responsible for most hemolytic cases for family studies almost invariably show one parent to have a benign elliptocytosis without evidence of hemolysis while the other parent is entirely normal. Genetic heterogeneity is suggested by linkage data but this does not explain all clinical variation, for severe hemolysis has been seen in both the Rh linked and nonlinked varieties. It has been suggested that hemolytic elliptocytosis may result from interaction of the elliptocytosis gene with other genetically determined defects and that the symptomatic patient is a double heterozygote. Although the postulated interacting genes usually have no phenotypic or biochemical expression, deficiencies of reduced glutathione and glucose-6-phosphate dehydrogenase (G6PD) have been suggested as operative in some hemolytic cases.

This report describes two pedigrees containing individuals with hemolytic elliptocytosis. In one family, double heterozygosity for the genes for G6PD deficiency and elliptocytosis did not result in hemolytic anemia. In the second family, a woman with benign elliptocytic trait had children with hemolytic elliptocytosis by two normal, unrelated fathers. The findings in this family and other recent reports make variable expression of a single dominant gene the best explanation for the spectrum of severity of the hemolytic manifestations associated with elliptocytosis.

Materials and Methods

Standard methods were used for routine hematologic determinations. Osmotic fragility and autohemolysin studies were done by Dacie's method. Hemoglobin electrophoresis

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HEREDITARY ELLIPTOCYTOSIS

Wallace Family—Daytona Beach, Florida

Fig. 1.—Pedigree Family 1.

was done at pH 8.6 on starch block. Fetal hemoglobin was estimated by means of the one minute alkali denaturation technic. G6PD was measured by the method of Zinkham. Reduced glutathione was measured by the method of Beutler. Blood groups were determined with commercial sera.

CASE REPORTS

Family 1 (Fig. 1): The propositus (11-3), a 3 8/12 year old Negro male was considered to be normal until 3 years of age when during hospitalization for pneumonia, he was found to be anemic. A diagnosis of sickle cell anemia was made because of anemia and a positive sickle cell preparation. Following recovery from pneumonia he was asymptomatic until a few weeks before admission when he developed persistent pain in the left upper abdomen. On admission to the hospital he was of normal height and weight. Positive physical findings included pallor of the mucous membranes, prominent frontal bossing and a firm tender spleen palpable 6 cm. below the left costal margin. X-ray revealed moderate widening of the diploic spaces of the skull. Hematologic studies are summarized in Table 1 and are compatible with a moderately severe hemolytic anemia. Red cell morphology was grossly abnormal with prominent ovalocytosis, spherocytosis and poikilocytosis.

Hemoglobin electrophoresis showed a Hgb A S pattern. Hgb S was 35 per cent and Hgb A2, 3.0 per cent. Hgb F by alkali denaturation was 1.8 per cent. G6PD level was elevated. Levels of reduced glutathione and glutathione stability were normal. Osmotic fragility was normal. After incubation the osmotic fragility curve shifted markedly to the right because of sickling of the red cells. Autohemolysis was slightly increased at 5.9 per cent; minimally correcting to 5.2 per cent with the addition of glucose. Bone marrow aspiration revealed normoblastic hyperplasia with a myeloid/erythroid ratio of 1/1. Serum haptoglobin was absent. $^{51}$CrT1/2 of the patient's red cell in his own circulation
<table>
<thead>
<tr>
<th>Patient</th>
<th>Hgb (Gm. 100 ml.)</th>
<th>Het. (%)</th>
<th>Retic. (%)</th>
<th>Smear</th>
<th>Hgb Elet. (eu. 100 ml. RBC)</th>
<th>Blood Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>I 1</td>
<td>13.2</td>
<td>42</td>
<td>2.6</td>
<td>Hypochromia, microcytosis</td>
<td>AA</td>
<td>cDe/ce</td>
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<td></td>
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<td></td>
<td>(7.2% A2)</td>
<td></td>
</tr>
<tr>
<td>I 2</td>
<td>12.0</td>
<td>36</td>
<td>0.8</td>
<td>Normal</td>
<td>AS</td>
<td>cDe/ce</td>
</tr>
<tr>
<td>I 3</td>
<td>11.5</td>
<td>35</td>
<td>1.2</td>
<td>Normal</td>
<td>AS 135</td>
<td>cDe/ce</td>
</tr>
<tr>
<td>I 4</td>
<td>14.1</td>
<td>43</td>
<td>1.5</td>
<td>Elliptocytosis</td>
<td>AA 15</td>
<td>cDe/ce</td>
</tr>
<tr>
<td>II 1</td>
<td>8.3</td>
<td>23</td>
<td>2.8</td>
<td>Hypo micro sickled</td>
<td>SSF</td>
<td>cDe/ce</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>(6.2% A2)</td>
<td></td>
</tr>
<tr>
<td>II 2</td>
<td>11.9</td>
<td>36</td>
<td>1.1</td>
<td>Normal</td>
<td>AA 62</td>
<td>cDe/ce</td>
</tr>
<tr>
<td>II 3a</td>
<td>6.6</td>
<td>22</td>
<td>9.8</td>
<td>Marked elliptocytosis</td>
<td>AS 295</td>
<td>cDe/ce</td>
</tr>
<tr>
<td>II b</td>
<td>9.2</td>
<td>26.5</td>
<td>6.7</td>
<td>—</td>
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<td>—</td>
</tr>
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was 6.5 days and 6.2 days when transfused to a normal recipient. Six days after injection of the tagged cells, the splenic to precordial ratio of ⁵¹Cr counts was 1.4 to 1; and the hepatic precordial ratio of counts was 1.9 to 1. Following transfusions of packed red cells, splenectomy was performed. The spleen was enlarged weighing 175 Gm. Congestion of the sinusoids by many elliptical cells was observed microscopically.

Four months after splenectomy the Hgb was 9.9 Gm. per cent, hematocrit 28.5 per cent and reticulocytes 5.6 per cent. The red cell morphology was even more bizarre than preoperatively. One year after splenectomy the hematocrit was 26.5 per cent and reticulocytes 6.7 per cent. Serum haptoglobin level was still 0 mg. per cent. The red cell morphology was more bizarre than preoperatively. Thus, splenectomy improved but did not completely correct the hemolytic process.

Family Study. The father, 1–4, had benign elliptocytosis and G6PD deficiency. No hematologic evidence of hemolysis was found. The mother, 1–3, had sickle cell trait but no elliptocytosis or hemolysis. A younger sister, 11–2, was heterozygous for G6PD deficiency, but otherwise normal. A cousin, 11–1, had typical Hgb S-β thalassemia disease but no elliptocytosis.

Family 2 (Fig. 2): The propositus was admitted to another hospital at the age of 5 years for correction of umbilical and right inguinal hernias. Anemia was found during preoperative study and a blood transfusion was given prior to surgery. At the age of 6 he was investigated for periorbital edema. Positive laboratory findings included Hgb of 6.7 Gm. per cent with reticulocyte count of 15 per cent. Elliptocytes were prominent on peripheral smear. Serum iron and hemoglobin electrophoresis were normal. The urinalysis, serum proteins, and urea nitrogen were normal. Within a few days the edema spontaneously regressed and no etiology for this episode was determined.

At the age of 7 years he was hospitalized for evaluation of anemia. Physical examination was negative except for an enlarged spleen palpable 4 cm. below the left costal margin.
Elliptocytosis with Hemolysis

Elliptocytosis without Hemolysis

Normal

Fig. 2.—Pedigree Family 2.

Laboratory data are listed on Table 2. Red cell morphology was remarkable for marked elliptocytosis. Hemoglobin electrophoresis, autohemolysis, and osmotic fragility studies were normal. Bone marrow aspiration showed erythroid hyperplasia. Red cell survival measured with 51DFP revealed a mean red cell life span of 14 days. G6PD level of reduced glutathione and glutathione stability were normal. Splenectomy was performed. The spleen weighed 125 Gm. and showed sinusoidal congestion with elliptical red cells. One year post splenectomy he was improved hematologically although the red cell morphologic changes were more extreme than preoperatively.

Table 2.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hgb. (Gm./100 ml.)</th>
<th>Hct. (%)</th>
<th>Retic. (%)</th>
<th>Smear</th>
<th>Hgb. Elect.</th>
<th>Blood Types</th>
<th>G6PD (c.u./100 ml RBC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15.5</td>
<td>51</td>
<td>0.6</td>
<td>Normal</td>
<td>AA</td>
<td>A eDe/ce</td>
<td>135</td>
</tr>
<tr>
<td>2</td>
<td>12.3</td>
<td>36</td>
<td>1.9</td>
<td>Moderate Ellipto.</td>
<td>AA</td>
<td>O eDe/ce</td>
<td>152</td>
</tr>
<tr>
<td>3</td>
<td>14.0</td>
<td>40</td>
<td>1.8</td>
<td>Normal</td>
<td>AA</td>
<td>B eDe/ce</td>
<td>130</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>8.0</td>
<td>a 24</td>
<td>3.7</td>
<td>Marked Ellipto.</td>
<td>AA</td>
<td>A eDe/ce</td>
<td>280</td>
</tr>
<tr>
<td>b*</td>
<td>10.1</td>
<td>b 32</td>
<td>1.6</td>
<td>AA</td>
<td>A eDe/ce</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>8.3</td>
<td>a 28</td>
<td>7.2</td>
<td>Marked Ellipto.</td>
<td>AA</td>
<td>B eDe/ce</td>
<td>300</td>
</tr>
<tr>
<td>3</td>
<td>11.3</td>
<td>34</td>
<td>2.0</td>
<td>Normal</td>
<td>AA</td>
<td>O eDe/ce</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>11.0</td>
<td>33</td>
<td>1.4</td>
<td>Normal</td>
<td>AA</td>
<td>O eDe/ce</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>11.0</td>
<td>32</td>
<td>1.2</td>
<td>Normal</td>
<td>AA</td>
<td>O eDe/ce</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>10.2</td>
<td>30</td>
<td>1.9</td>
<td>Slight Hypochro.</td>
<td>AA</td>
<td>O eDe/ce</td>
<td></td>
</tr>
</tbody>
</table>

*Post-splenectomy values.
Family Study. The patient’s older half-brother, 11-1, had hematologic findings very similar to those of the propositus. Splenectomy was also performed on this boy with comparable improvement. The mother, 1-2, had elliptical red cells but no evidence of hemolysis. Four younger siblings of the propositus did not have elliptocytosis, anemia, or evidence of hemolysis. The two unrelated fathers, 1-1 and 1-3, were both hematologically normal.

Discussion

The genetic basis of most cases of hemolytic elliptocytosis is controversial. The findings in Family 1 do not support the suggestion that interaction of the genes for G6PD deficiency and elliptocytosis results in hemolytic elliptocytosis. The father in this pedigree who had both elliptocytic red cells and low levels of G6PD did not have evidence of hemolysis. The propositus had the expected high levels of G6PD seen in hemolytic anemias with high reticulocyte counts. The gene for G6PD deficiency, S, C, and thalassemia does not appear to interact with the elliptocytosis gene to augment clinical and hematologic severity. Since G6PD deficiency occurs in about 10 per cent of Negro males, elliptocytosis may be expected on occasion to occur coincidentally with enzyme deficiency. The fact that the propositus had sickle cell trait is considered coincidental reflecting the 8 per cent prevalence of the sickle cell in Florida Negroes. Noninteraction of the traits has been repeatedly described and this laboratory has studied 2 additional cases unrelated to the present ones with sickle trait and benign elliptocytosis.

In the second family a woman with benign elliptocytosis without a hemolytic component had children with identical hemolytic elliptocytosis. These children were progeny of two unrelated and hematologically normal fathers. It is unlikely that both of these unrelated men would possess and transmit the same type of unapparent but interacting gene.

Variability of expression is a cardinal characteristic of dominant genes. That variable expression of a single dominant gene is the basis for the spectrum of clinical severity of the elliptocytic syndrome is supported by an extensive pedigree recently described in Iceland. Forty-five individuals with elliptocytosis were identified as having descended from a single ancestor, thus they presumably possessed the same gene. In this pedigree, although genetic heterogeneity was not present, a very wide spectrum of hematologic severity was seen. This ranged from moderate elliptocytosis with otherwise normal hematologic status to frank hemolytic anemia with markedly abnormal red cell morphology. Similar intrafamily variability was seen in a small pedigree from Australia.

A precise biochemical lesion or mechanism in elliptocytosis has not been ascertained. Zipursky has described increased membrane permeability to sodium of the red cells of patients with nonhemolytic elliptocytosis. No studies in hemolytic cases have been described. If a precise biochemical or enzymatic defect can be delineated, a quantitative definition of genotype may be possible. Until this is accomplished, classic pedigree analysis can provide important evidence bearing on modes of inheritance and possibility of more recondite hypotheses such as isoallelic modification. The pedigrees described
here reinforce the concept that variable expression of a single dominant gene is responsible for the spectrum of clinical severity in the hereditary elliptocytic syndromes.

**Summary**

Two pedigrees containing cases of hemolytic elliptocytosis provide insight into the genetic basis of hemolytic elliptocytosis. One demonstrates non-interaction of genes for G6PD elliptocytosis. In the second, a woman with benign elliptocytosis had children with hemolytic elliptocytosis by two unrelated fathers. Variable expression of a dominant gene is supported as the most likely explanation for the variability of spectrum of clinical severity in the hereditary elliptocytic syndromes.

**SUMMARY IN INTERLINGUA**

Duo arbores genealogic continente casos de elliptocytose hemolytic esseva studiate con respecto al information providite per illos relative al bases genetic de elliptocytose hemolytic. Le un del arbores demonstra le noninteraction de genes pro elliptocytose a G6PD. In le secunde, un femina con elliptocytose benigna habeva pueros con elliptocytose hemolytic per duo nonrelationate patres. Le these de un expression variabile de un gen dominante es supportate como le explication le plus probabile pro le variabilitate del spectro de severitate clinic in le syndromes elliptocytic hereditari.

**REFERENCES**

16. Aksoy, M.: The combination of her-


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