Combination of Hereditary Elliptocytosis and Heterozygous Beta-thalassaemia: A Family Study*

MUZAFFER AKSOY and ŞAKIR ERDEM

From Second Internal Clinic of Istanbul Medical School, Istanbul, Turkey

Hereditary elliptocytosis has been described in sporadic association with β-thalassaemia (Brumpt, Delabarre, and De Traverse, 1960; De Vries, De Jong, and Frenkel, 1959; Aksoy, 1963; Perilli and Chernoff, 1965; Angelopoulos and Caralis, 1965). With the exception of two cases reported by Perilli and Chernoff (1965) and Angelopoulos and Caralis (1965), the combination of hereditary elliptocytosis and heterozygous β-thalassaemia has not been described in association with mutual enhancement of any of the involved genes. On the other hand, according to Perrillie and Chernoff (1965) and Angelopoulos and Caralis (1965), there is suggestive evidence that the clinical effects of both genes are summated or the expressivity of the involved genes enhanced when they are both present in the same individual.

Recently we have investigated a Turkish family with hereditary elliptocytosis in association with β-thalassaemia. Of 9 sibs investigated, 3 had the combination of these 2 genes. Interestingly, in these 3 patients with the combination of hereditary elliptocytosis and heterozygous β-thalassaemia there were some clinical manifestations and haematological findings which suggested the possibility of a mutual enhancement of some of the genes involved.

Material and Methods

The haematological methods were standard. Haemoglobin analyses were performed by starch gel electrophoresis, using borate buffer at pH 8-6 according to the method of Smithies (1955) and slightly modified by Aksoy and Erdem (1965). Hb F was determined by the method of Singer, Chernoff, and Singer (1951); and quantitative estimations of Hb A2 by the method of DEAE-cellulose chromatography following the descriptions of Huisman and Dozy (1961). The relative concentrations of haemoglobin solutions were finally estimated in a Unicam spectrophotometer at 415 mμ. Measurement of erythrocyte glucose-6-phosphate-dehydrogenase activity was determined by the method of Gadsden and Cannon (1964). Faecal urobilinogen was determined by the method of Young, Davis, and Hogestyn (1949) using a comparator block.† In this method normal values for faecal urobilinogen are 50 to 300 Ehrlich Units per 100 g. faeces.

Family Report

The family was of Turkish origin and living in a village of Dörtöyl near Iskenderun. Haematological data for each family member examined are summarized in the Table. The family pedigree is shown in Fig. 1.

The propositus (II.3), a 19-year-old Dental School student, came to our laboratory for haemoglobin analysis. He had been anaemic and icteric from early childhood, and suffered from easy fatigability, particularly after a sleepless night. Physical examination revealed a well-developed, well-nourished boy with subicteric sclera and pallor. The spleen was enlarged two finger-breadths below the costal margin. There were no other abnormal findings. The patient’s laboratory data are summarized in the Table. A decreased osmotic fragility curve was obtained by quantitative erythrocyte osmotic fragility before and after 24 hours’ incubation at 37° C. Total bilirubin was 2:1 mg./100 ml., all of which was indirect reacting. Serum iron was 81 μg/100 ml.; reticulocytes 4-5%; G6PD activity was 157 units/100 ml. erythrocytes (normal level for men 135–189 units/100 ml. erythrocytes). A bone survey and a cholecystography revealed no abnormalities.

Blood samples and blood smears from the parents and 8 sibs were sent directly from their village. Haematological data for each family member studied are also recorded in the Table.

Discussion

The existence of a β-thalassaemia gene in the propositus can be seen clearly from the case report, the Table, and Fig. 1. The criteria are as follows:

† Manufactured by M. A. Taylor Co., Baltimore, Md.
Combination of Hereditary Elliptocytosis and Heterozygous Beta-thalassaemia: A Family Study

**Fig. 1.** Pedigree of a family with the combination of hereditary elliptocytosis and heterozygous β-thalassaemia.

**TABLE**

<table>
<thead>
<tr>
<th>Pedigree and Designation</th>
<th>Hb (g./100 ml.)</th>
<th>RBC/10^6</th>
<th>Haematocrit (%)</th>
<th>MCV μg</th>
<th>MCH γ</th>
<th>Target Cells</th>
<th>Ovalocytosis</th>
<th>Elliptocytosis</th>
<th>Microcytosis</th>
<th>Hypochromia</th>
<th>Poikilocytosis</th>
<th>Hb F %</th>
<th>Hb A2 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. 1</td>
<td>12.3</td>
<td>5.30</td>
<td>44</td>
<td>82</td>
<td>23</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>I. 2</td>
<td>13.0</td>
<td>3.90</td>
<td>37</td>
<td>94</td>
<td>30</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>0.2</td>
<td>2.3</td>
</tr>
<tr>
<td>II. 3</td>
<td>9.1</td>
<td>4.90</td>
<td>37</td>
<td>75</td>
<td>18</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>9.0</td>
<td>4.2</td>
</tr>
<tr>
<td>II. 4</td>
<td>11.0</td>
<td>4.95</td>
<td>38</td>
<td>81</td>
<td>22</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>4.4</td>
<td>5.4</td>
</tr>
<tr>
<td>II. 5</td>
<td>13.0</td>
<td>4.80</td>
<td>42</td>
<td>87</td>
<td>27</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>1.7</td>
<td>2.6</td>
</tr>
<tr>
<td>II. 6</td>
<td>9.4</td>
<td>4.60</td>
<td>38</td>
<td>82</td>
<td>24</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>8.5</td>
<td>4.5</td>
</tr>
<tr>
<td>II. 7</td>
<td>13.5</td>
<td>4.80</td>
<td>43</td>
<td>89</td>
<td>28</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0.2</td>
<td>2.8</td>
</tr>
<tr>
<td>II. 8</td>
<td>12.0</td>
<td>4.80</td>
<td>39</td>
<td>80</td>
<td>25</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>3.3</td>
<td>4.9</td>
</tr>
<tr>
<td>II. 9</td>
<td>12.5</td>
<td>4.85</td>
<td>44</td>
<td>91</td>
<td>26</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>0.3</td>
<td>3.0</td>
</tr>
<tr>
<td>II. 11</td>
<td>11.0</td>
<td>4.80</td>
<td>39</td>
<td>80</td>
<td>21</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>2.4</td>
<td>4.6</td>
</tr>
<tr>
<td>II. 12</td>
<td>9.4</td>
<td>4.60</td>
<td>37</td>
<td>80</td>
<td>20</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>7.5</td>
<td>4.6</td>
</tr>
</tbody>
</table>

raised levels of Hb A2 and Hb F, hypochromia, microcytosis, poikilocytosis, targeting, decreased red cell fragility, and normal serum iron level. On the other hand, the marked elliptocytosis in the blood smear (Fig. 2) was an indication for the possible presence of the elliptocytic gene in the propositus.* The final proof of this possibility was provided by the results of the genetic study. The father had the stigmata of hereditary β-thalassaemia, i.e. decreased mean corpuscular volume and mean corpuscular Hb, microcytosis, hypochromia, targeting (Fig. 2), and particularly increased levels of Hb A2 and F. On the other hand, the mother had the morphological criteria characteristic of hereditary elliptocytosis (Fig. 2). Of 12 offspring, 9 were investigated (Fig. 1). Two of them (II.5 and II.7) were normal. One (II.9) had, like her mother, an asymptomatic form of hereditary elliptocytosis. Three sibs (II.4, II.8, and II.11) had, like their father, the above-mentioned haematological findings of heterozygous β-thalassaemia. In addition to the propositus (II.3), 2 other sibs (II.6 and II.12) had the combination of hereditary elliptocytosis and heterozygous β-thalassaemia. The criteria are as follows: decreased mean corpuscular volume and mean corpuscular Hb, increased levels of foetal Hb and Hb A2, hypochromia, microcytosis, poikilocytosis, targeting, and marked elliptocytosis.

*We noticed that some of the elliptocytes or ovalocytes also showed target cell form. We might call these, ellipto-target cells see Fig. 2.

If we compare the clinical manifestations and haematological findings of the propositus, his 2 similar sibs (II.6 and II.12), and those of the other members of his family (Table), there is strong reason for supposing that there was a mutual enhancement of the expressivity of the involved genes in this family, with the combination of hereditary elliptocytosis and heterozygous β-thalassaemia. The criteria supporting this assumption are as follows (1) **Level of haemoglobin:** though the level in the family members carrying one gene responsible either for hereditary elliptocytosis or β-thalassaemia (I.1, I.2, II.4, II.8, II.9, and II.11) was not less...
than 11 g./100 ml., the level in 3 patients with the combination of hereditary elliptocytosis and heterozygous $\beta$-thalassaemia (II.3, II.6, and II.12) was less than 10, 9-1, and 9-4 g./100 ml., respectively.

(2) Level of foetal haemoglobin: though the level found in 4 family members with heterozygous $\beta$-thalassaemia (I.1, II.4, II.8, and II.11) was less than 5% (mean foetal concentration 3-8%), the content of foetal Hb was more than 5% (mean concentration 8-3%, little more than twice the former value) in 3 sibs with the combination of hereditary elliptocytosis and heterozygous $\beta$-thalassaemia (II.3, II.6, and II.12), 9, 8-5, and 7-5%, respectively. This is particularly significant in view of the reported intrafamilial similarity of the levels of Hb F in thalassaemia.

Bearing these facts in mind, we think that the uncompensated haemolytic anaemia present in the propositus is the result of the mutual enhancement of any of the involved genes, namely the genes responsible for hereditary elliptocytosis and $\beta$-thalassaemia. On the other hand, most of the previous reports concerning the combination of hereditary elliptocytosis and heterozygous $\beta$-thalassaemia did not appear to show this mutual enhancement (Brumpt et al., 1960; De Vries et al., 1959; Aksoy, 1963). On the contrary, the uncompensated haemolytic anaemia found in the patients with the combination of hereditary elliptocytosis and heterozygous $\beta$-thalassaemia represents either a summation of the clinical effects of the involved genes (Perillie and Chernoff, 1965), or the expressivity of the gene for hereditary elliptocytosis is affected by some of the genes responsible for $\beta$-thalassaemia (Angelopoulos and Caralis, 1965).

If one compares the previous descriptions of the combination of hereditary elliptocytosis and heterozygous $\beta$-thalassaemia by Brumpt et al. (1960), De Vries et al. (1959), and Aksoy (1963), with those of Perillie and Chernoff (1965) and Angelopoulos and Caralis (1965), and the present family, haemoglobinopathy can be classified into two types. (1) The combination of hereditary elliptocytosis and heterozygous $\beta$-thalassaemia without mutual enhancement of the involved genes. (2) The combination of hereditary elliptocytosis and heterozygous $\beta$-thalassaemia with either a summation of the clinical effects of the genes or mutual enhancement of any of the involved genes.

This may be explained by the existence of more than one kind of gene for $\beta$-thalassaemia and hereditary elliptocytosis.

Summary

Some of the members of the family reported in
Combination of Hereditary Elliptocytosis and Heterozygous Beta-thalassaemia: A Family Study

this paper have either a β-thalassaemia or a hereditary elliptocytosis gene alone, while others show a combination of these two genes. In 3 sibs with the combination of these two genes, haematological findings suggest a mutual enhancement of the effects of these two particular genes present in this family. Considering also other reported cases, the authors think that the combination of hereditary elliptocytosis and β-thalassaemia should be divided into two types, according to whether these two genes show a mutual enhancement of their effects or not.

REFERENCES


Combination of hereditary elliptocytosis and heterozygous beta-thalassaemia: a family study.
M Aksoy and S Erdem

J Med Genet 1968 5: 298-301
doi: 10.1136/jmg.5.4.298

Updated information and services can be found at:
http://jmg.bmj.com/content/5/4/298.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/