Interaction of α- and δβ0-thalassaemia: haematological features and globin chain synthesis analysis

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SUMMARY An observation of suspected interaction of δβ0- and α-thalassaemia, identified through careful examination of the family, is reported. The δβ0-thalassaemia was of the usual type found in Sardinia, characterised by high Hb F levels and very low levels of glycine in the isolated γCB3 peptide. The haematological findings in the double δβ0-α-thalassaemia heterozygotes were: normal MCV and Hb A2 levels, increased Hb F (11.3 to 16.8%) heterogeneously distributed in red cells, and almost balanced α/β globin chain synthesis ratios.

Hereditary persistence of fetal haemoglobin (HPFH) and δβ0-thalassaemia are closely related groups of genetic disorders of haemoglobin synthesis, characterised by an effective increase of γ chain production, as shown by the high Hb F levels in heterozygotes. Therefore, there are considerable difficulties in the differential diagnosis of these disorders, particularly those involving the Gγ types. In fact, in the heterozygous state there is a large overlap in haematological criteria (normal red cell indices in HPFH versus low MCH and MCV in δβ0-thalassaemia), globin chain synthesis ratios (balanced versus unbalanced), and haemoglobin F distribution (pancellular versus heterocellular) in both conditions. However, this differentiation has very important practical implications in genetic counseling, since β or δβ0 × δβ0 heterozygous thalassaemia mating is associated with the risk of producing thalassaemia major or intermedia in the offspring, while HPFH × β or δβ0 mating involves no such risk.

In this paper we report an observation of suspected interaction of δβ0- and α-thalassaemia which created some difficulties in the counselling of a couple attending our genetic clinic.

Case report

In 1978 a couple presented at our genetic service for counselling. The husband was a high Hb A2 β-thalassaemia carrier (III.1) and the wife (III.2) had normal MCV and Hb A2 levels, increased Hb F (>5%) heterogeneously distributed in red cells, and an almost balanced α/β globin chain synthesis ratio. The table shows the haematological features of this couple and some other family members and the figure depicts the family tree.

As can be seen in the figure, the father (II.1) is normal and the mother (II.2) is similar both haematologically and in globin chain synthesis ratio to her daughter (III.2). The grandfather (I.1) had reduced MCV, Hb A2 levels, and α/β ratio (0.60), as in the α-thalassaemia carrier state (α-thalassaemia-1). The

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Hb</th>
<th>RBC</th>
<th>MCV</th>
<th>MCH</th>
<th>Hb A2</th>
<th>Hb F</th>
<th>α/β</th>
<th>α/β + γ</th>
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<tr>
<td>I.1</td>
<td>78</td>
<td>14.7</td>
<td>5.06</td>
<td>76</td>
<td>29</td>
<td>1.99</td>
<td></td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>I.2</td>
<td>76</td>
<td>11.5</td>
<td>4.66</td>
<td>77</td>
<td>24.6</td>
<td>2.29</td>
<td>11.3</td>
<td>1.68</td>
<td>1.35</td>
</tr>
<tr>
<td>II.1</td>
<td>51</td>
<td>14.8</td>
<td>4.80</td>
<td>93</td>
<td>30.8</td>
<td>2.92</td>
<td>0.80</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>II.2</td>
<td>49</td>
<td>13.8</td>
<td>5.14</td>
<td>78</td>
<td>26.8</td>
<td>2.14</td>
<td>14.1</td>
<td>1.14</td>
<td>1.01</td>
</tr>
<tr>
<td>III.1</td>
<td>35</td>
<td>14.2</td>
<td>6.51</td>
<td>66</td>
<td>21.8</td>
<td>4.48</td>
<td>0.90</td>
<td>—</td>
<td>—</td>
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<tr>
<td>III.2</td>
<td>26</td>
<td>14.0</td>
<td>5.27</td>
<td>80</td>
<td>26.5</td>
<td>2.40</td>
<td>16.8</td>
<td>1.27</td>
<td>1.11</td>
</tr>
<tr>
<td>III.3</td>
<td>20</td>
<td>12.7</td>
<td>5.01</td>
<td>72</td>
<td>25.3</td>
<td>2.24</td>
<td>16.3</td>
<td>2.48</td>
<td>2.00</td>
</tr>
</tbody>
</table>

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Model S. Haemoglobin electrophoresis was carried out on cellulose acetate plate (Titan III, Helena Laboratories, Beaumont, Texas). Hb A₂ was quantified by DE-52 microchromatography and Hb F by alkaline denaturation. The distribution of Hb F in erythrocytes was shown using the acid elution technique of Kleihauer et al. Biosynthetic ratios were determined from peripheral blood according to Kan et al and expressed as specific activity. Hb F structural studies were performed as previously described.

**Discussion**

The haematological features (table) (normal red cell indices, increased Hb F heterogeneously distributed in red cells, and balanced globin chain synthesis ratio) found in one member of this couple (III.2) are consistent with a diagnosis of heterocellular HPFH or δβ⁰-thalassaemia carrier state. Information for differentiating between these two conditions was obtained by the study of the family tree.

The father (II.1) had normal results and the mother (II.2) showed haematological characteristics similar to those of her daughter (III.2). However, the grandfather (I.1) had haematological features compatible with the α-thalassaemia carrier state (α-thalassaemia-1) while the grandmother (I.2) and the wife's brother (III.3) had phenotypic manifestations consistent with a diagnosis of δβ⁰-thalassaemia (low MCV and MCH, increased Hb F heterogeneously distributed in red cells, and increased α/β globin chain synthesis ratio).

Therefore, it can be assumed that the wife (III.2) and her mother (II.2) had inherited the δβ⁰-thalassaemia gene from the grandmother (I.2) together with the α-thalassaemia-1 gene from the grandfather (I.1). The presence of δβ⁰- and α-thalassaemia-1 genes determined an almost balanced globin chain synthesis ratio. It should be pointed out that Sardinian δβ⁰-thalassaemia carriers have always been found to have unbalanced α/β chain synthesis ratios at variance with the findings of Kinney et al who reported α/β ratios overlapping those of normal subjects in a group of Negro and Caucasian δβ⁰-thalassaemia carriers.

The above interpretation is likely to be correct, but DNA restriction enzyme analysis should be carried out for confirmation.

The normal MCV in the wife and her mother is compatible with the δβ⁰-thalassaemia carrier state, since in the Sardinian population a large overlap between MCV and MCH values of δβ⁰-thalassaemia carriers and those of normal subjects has been found.

**Methods**

Red blood cell indices from venous blood collected in EDTA were estimated with Coulter Counter

**Figure** Family pedigree.

**NOTE:**

1. Haemoglobin electrophoresis was carried out on cellulose acetate plate (Titan III, Helena Laboratories, Beaumont, Texas)
2. Hb A₂ was quantified by DE-52 microchromatography and Hb F by alkaline denaturation
3. Biosynthetic ratios were determined from peripheral blood according to Kan et al
4. Hb F structural studies were performed as previously described
5. The father (II.1) had normal results and the mother (II.2) showed haematological characteristics similar to those of her daughter (III.2)
6. However, the grandfather (I.1) had haematological features compatible with the α-thalassaemia carrier state (α-thalassaemia-1) while the grandmother (I.2) and the wife's brother (III.3) had phenotypic manifestations consistent with a diagnosis of δβ⁰-thalassaemia (low MCV and MCH, increased Hb F heterogeneously distributed in red cells, and increased α/β globin chain synthesis ratio)
7. Therefore, it can be assumed that the wife (III.2) and her mother (II.2) had inherited the δβ⁰-thalassaemia gene from the grandmother (I.2) together with the α-thalassaemia-1 gene from the grandfather (I.1)
8. The presence of δβ⁰- and α-thalassaemia-1 genes determined an almost balanced globin chain synthesis ratio
9. It should be pointed out that Sardinian δβ⁰-thalassaemia carriers have always been found to have unbalanced α/β chain synthesis ratios at variance with the findings of Kinney et al who reported α/β ratios overlapping those of normal subjects in a group of Negro and Caucasian δβ⁰-thalassaemia carriers
10. The above interpretation is likely to be correct, but DNA restriction enzyme analysis should be carried out for confirmation
11. The normal MCV in the wife and her mother is compatible with the δβ⁰-thalassaemia carrier state, since in the Sardinian population a large overlap between MCV and MCH values of δβ⁰-thalassaemia carriers and those of normal subjects has been found
12. In conclusion this study exemplifies the difficulties
involved in the differential diagnosis of HPFH and $\beta^0$-thalassaemia, and in particular the necessity of carrying out family studies for the identification of the $\alpha/\beta^0$ interaction.

References

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