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.1 Therefore, there are considerable difficulties in the differential diagnosis of these disorders, particularly those involving the Gγ types.2-10 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.2-13 However, this differentiation has very important practical implications in genetic counselling, 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.I) had reduced MCV, Hb A2 levels, and α/β ratio (0·60), as in the α-thalassaemia carrier state (α-thalassaemia-1). The

<table>
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<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>
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<td>5.06</td>
<td>76</td>
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<td>—</td>
<td>0.60</td>
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<tr>
<td>I.2</td>
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<td>11.5</td>
<td>4.66</td>
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<td>4.80</td>
<td>93</td>
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<td>0.80</td>
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<td>5.14</td>
<td>78</td>
<td>26.8</td>
<td>2.14</td>
<td>14.1</td>
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<td>66</td>
<td>21.8</td>
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<td>0.90</td>
<td>—</td>
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<tr>
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<td>5.27</td>
<td>80</td>
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<tr>
<td>III.3</td>
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<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>
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</table>

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<th></th>
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<tbody>
<tr>
<td>I</td>
<td>MCV fl</td>
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<td>2</td>
</tr>
<tr>
<td></td>
<td>Hb A2 (%)</td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Hb F (%)</td>
<td>1:99</td>
<td>2:29</td>
</tr>
<tr>
<td>α/β</td>
<td>0:60</td>
<td>1:13</td>
<td></td>
</tr>
<tr>
<td>α/ non-α</td>
<td>1:35</td>
<td></td>
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</tr>
</tbody>
</table>

| II | MCV fl | 1 | 2 |
|   | Hb A2 (%) | 93 | 78 |
|   | Hb F (%) | 2:92 | 2:4 |
| α/β | 1:27 | 1:07 |
| α/ non-α | 1:41 |

| III | MCV fl | 1 | 2 |
|     | Hb A2 (%) | 4:48 | 2:40 |
|     | Hb F (%) | 16.8 | 16.3 |
| α/β | 1:27 | 2:48 |
| α/ non-α | 1:41 |

α-thal heterozygote  β-thal heterozygote  Normal  δβ0-thal heterozygote  Not examined

The family pedigree.

grandmother (I.2) and the wife’s brother (III.3) had classic manifestations of heterozygous δβ0-thalassaemia with reduced MCV, normal Hb A2 levels, increased Hb F levels heterogeneously distributed in red cells, and increased α/β ratio. This family shows the δβ0-thalassaemia type, characterised by unusually high Hb F levels (range 10 to 20 %) and a very low glycine content (range 0-02 to 0-14 residues) in the isolated γCB3 peptide (determination kindly performed by Dr L F Bernini, Leiden, Holland), as seen in all Sardinian δβ0 carriers studied till now.13 In II.2 and III.2 the glycine content in the isolated γCB3 peptide was 0-04 and 0-06, respectively.

During a later counselling session, the couple was informed that there was a 25% risk of thalassaemia intermedia (δβ0/β0-thalassaemia genetic compound) in their offspring. The predicted mildness of the disease was stressed. The couple decided on a pregnancy monitored by antenatal diagnosis.

Methods

Red blood cell indices from venous blood collected in EDTA were estimated with Coulter Counter model S. Haemoglobin electrophoresis was carried out on cellulose acetate plate (Titan III, Helena Laboratories, Beaumont, Texas). Hb A2 was quantified by DE-52 microchromatography11 and Hb F by alkali denaturation.15 The distribution of Hb F in erythrocytes was shown using the acid elution technique of Kleihauer et al.16 Biosynthetic ratios were determined from peripheral blood according to Kan et al15 and expressed as specific activity. Hb F structural studies were performed as previously described.18

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,18 at variance with the findings of Kinney et al11 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.13

In conclusion this study exemplifies the difficulties
involved in the differential diagnosis of HPFH and δβ-thalassaemia, and in particular the necessity of carrying out family studies for the identification of the α/δβ interaction.

References


Requests for reprints to Professor Antonio Cao, Clinica Pediatrica II, C/Post 251, Via Porcell 1, 09100 Cagliari, Sardinia, Italy.
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