\(\alpha\)-thalassaemia in Sardinian infants

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SUMMARY A haemoglobin survey carried out in southern Sardinian newborn infants showed an overall incidence of 12.9% with haemoglobin Bart's of more than 1%. The distribution was trimodal: low (1 to 2%), intermediate (2 to 10%), and high (about 25%). A considerable overlap was seen between the first two groups. Both the 1 to 2% and 2 to 10% groups had thalassaemia-like red cell indices at birth. Newborn infants ascertained as having \(\alpha\)-thalassaemia at follow-up did not necessarily have unbalanced \(\alpha\)/non-\(\alpha\) chain synthesis at birth. At follow-up examination two subjects in the 25% group had developed haemoglobin H disease, and the 2 to 10% group had thalassaemia-like red cell indices and unbalanced globin chain synthesis ratios indicative of heterozygous \(\alpha\)-thalassaemia. The 1 to 2% group either had normal or slightly reduced \(\alpha\)-chain synthesis ratios, indicative of the silent \(\alpha\)-thalassaemia carrier state. Two subjects with 2.0% and 2.5% haemoglobin Bart's at birth had heterozygous \(\beta\)-thalassaemia at follow-up. Therefore, they were double heterozygotes for \(\alpha\) and \(\beta\)-thalassaemia with \(\alpha/\beta\)-globin chain synthesis ratios of 0.81 and 0.86. Genotype assessment in a few families showed that infants with haemoglobin Bart's levels of more than 2% may have one of the genotypes \(-\alpha/-\alpha\) or \(-/-\alpha\alpha\).

The \(\alpha\)-thalassaemias (\(\alpha\)-thal) are a group of genetic disorders resulting from defective \(\alpha\)-chain synthesis, which occur in many populations including Chinese, Thai, Italian, and Negro.1-5

In Asian populations four \(\alpha\)-thalassaemia syndromes of increasing clinical severity have been recognised2: (1) the silent carrier state (\(\alpha\)-thal 2) with no clinical manifestation and 1 to 2% \(Hb\) Bart's at birth; (2) heterozygous \(\alpha\)-thalassaemia (\(\alpha\)-thal 1), characterised by thalassaemia-like red cell indices and 5 to 6% \(Hb\) Bart's at birth; (3) \(Hb\) H disease, with haemolytic anaemia and 25 to 30% \(Hb\) Bart's at birth; and (4) homozygous \(\alpha\)-thalassaemia which manifests as hydrops fetalis. These four syndromes depend on the deletion of from one to all four copies of the \(\alpha\)-globin structural genes (\(-\alpha/\alpha\alpha; -/-\alpha\alpha; -/-\alpha\alpha; -/-\alpha\alpha\)).5-11

In Mediterranean populations \(\alpha\)-thalassaemia is relatively common and \(Hb\) H disease is frequently found, but hydrops fetalis is rare.12-13

Information on the genetics and incidence of \(\alpha\)-thalassaemia in Sardinia is scarce. A 6.9% carrier rate was recently found in a thalassaemia screening programme directed at the adult population.5 \(Hb\) H disease was frequently observed14 and this may be the result of a deletion defect (\(-/\alpha\alpha\)) or a combination of a deletion and non-deletion defect (\(\alpha\thalo/--\)).15 Hydrops fetalis has never been found (unpublished results).

In this paper we describe: (1) a survey of the haemoglobins of Sardinian newborn infants; (2) a prospective evaluation of the significance of \(Hb\) Bart's, with haematological and globin chain synthesis analysis in children who had variable levels of \(Hb\) Bart's at birth; and (3) a study of the genetic transmission pattern in a few families with a proband with high \(Hb\) Bart's at birth.

Materials and methods

SUBJECTS PARTICIPATING IN THE STUDY

Capillary blood for cellulose acetate electrophoresis was obtained by heel puncture from 2291 term infants born in the Obstetrics and Gynecology Department of Cagliari University. This Obstetric service takes care of the southern Sardinian population handling about 3500 deliveries per year. The samples were taken from consecutive deliveries from January to August 1976. This material is therefore a representative sample of the southern Sardinian population.
A venous blood sample for quantitative Hb Bart's evaluation was obtained on the second postnatal day from 143 newborn infants showing the presence of this Hb fraction on visual inspection of the cellulose acetate plate. In the remaining 152 subjects showing Hb Bart's, a venous blood sample could not be obtained. Therefore, they were classified as having high (about 25%), intermediate (2 to 10%), or low (1 to 2%) Hb Bart's by visual inspection.

A total of 49 newborn infants with zero or variable Hb Bart's levels had red cell indices studies. Five of these, with Hb Bart's ranging from 2.3 to 7.6%, also had globin chain synthesis analysis.

Children who had been tested for the presence of Hb Bart's at birth had red cell indices and globin chain synthesis analysis (20 cases) or only red cell indices (41 cases) at 9 to 28 months.

In four cases haematological and globin chain synthesis analysis was also carried out in the parents.

DETECTION OF HB BART'S
Haemoglobin analysis was carried out by electrophoresis on Titan III cellulose acetate plates (Helena Laboratories, Beaumont, Texas) using tris-EDTA borate buffer, pH 8.4.

Red cell lysates were prepared by adding one drop of packed red cells, collected in heparinised capillary tubes, to 3 to 4 drops of the haemolysate reagent (Helena Laboratories).

The nature of the fast moving haemoglobin component, detected in many samples, was determined after isolation by starch block electrophoresis, by means of globin chain electrophoresis on cellulose plates in urea 2 mercaptoethanol buffer, pH 8-9 and pH 6-5, according to Schneider.16

The quantification of Hb Bart's was carried out in duplicate by starch-block electrophoresis using an 0.05 mol/l phosphate buffer system, pH 7-0. For this quantification, haemolysates were prepared from heparinised venous blood, washed three times with physiological saline solution, and then lysed by addition of 1 volume of water and 0.4 volumes of toluene.

The haemoglobin fractions were eluted and their relative proportion determined according to Weatherall and Clegg.1

HAEMATOLOGICAL STUDIES
Red cell indices were obtained with Coulter Counter model ZBI and Coulter Hemoglobinimeter. Hb A2 was quantified by column microchromatography.17

Globin chain synthesis analysis was performed according to Kan et al.18

RESULTS
ACCURACY OF THE SCREENING METHOD
Serial dilution of a sample with 5.0% Hb Bart's was made with a haemolysate prepared from a normal adult. This material was analysed by cellulose acetate electrophoresis at pH 8.4. This experiment showed that Hb Bart's was clearly visible only at 1% concentration of the total haemoglobin. On the other hand, quantification of Hb Bart's by starch-block electrophoresis of samples showing the presence of the component on cellulose acetate electrophoresis consistently showed a concentration higher than 0.98%. Therefore, it was assumed that the absence of an easily distinguishable band of Hb Bart's on cellulose acetate electrophoresis indicates a concentration of this haemoglobin compound lower than 1%.

INCIDENCE, AMOUNT, AND DISTRIBUTION OF HB BART'S
Haemoglobin Bart's was detected by cellulose acetate electrophoresis (fig 1) in 295 of 2291 newborn infants, an overall incidence of 12.9%.

In the group of subjects (143) who had Hb Bart's quantification by starch block electrophoresis, the amount varied from 0.98 to 26.14% of the total haemoglobin concentration.

As can be seen in fig 2 the distribution seems to be trimodal with a large overlap between the two groups with low (1 to 2%) and intermediate (2 to 10%) Hb Bart's levels.

In the group of subjects classified by visual inspection, 115 had low Hb Bart's levels and 37 had intermediate levels. Therefore, considering the two groups as one, the total percentages of subjects with low Hb Bart's (1 to 2%) and intermediate Hb Bart's (2 to 10%) were 7.0% and 5.6%, respectively. Five infants, including a couple of monozygotic twins, had high Hb Bart's levels (22.0 to 26.1%).

HB BART'S AND RED CELL INDICES IN NEWBORN INFANTS
Newborn infants with 2 to 10% Hb Bart's had

![Figure 1: Cellulose acetate electrophoresis, pH 8.4, of newborn infants' Hb showing two subjects with intermediate levels (2-10%) of Hb Bart's.](http://jmg.bmj.com/Downloaded from http://jmg.bmj.com/)
**α-thalassaemia in Sardinian infants**

![Graph showing Hb Bart's levels in Sardinian newborn infants.]

**TABLE 1** Red cell indices (mean ± 1 SD) and statistical evaluation in newborn infants with variable amounts of Hb Bart’s

<table>
<thead>
<tr>
<th>Subjects (No of cases)</th>
<th>RBC (x10^12/l)</th>
<th>Hb (g/dl)</th>
<th>Hct (%)</th>
<th>MCV (fl)</th>
<th>MCH (pg)</th>
<th>MCHC (%)</th>
<th>Hb Bart’s (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Newborn infants without Hb Bart’s (15)</td>
<td>5.64 ± 0.42</td>
<td>20.5 ± 1.4</td>
<td>60.7 ± 4.2</td>
<td>108.3 ± 4.6</td>
<td>36.8 ± 2.1</td>
<td>33.6 ± 0.7</td>
<td>—</td>
</tr>
<tr>
<td>(2) Newborn infants with 1–2% Hb Bart’s (13)</td>
<td>5.61 ± 0.59</td>
<td>18.4 ± 2.1</td>
<td>54.6 ± 5.6</td>
<td>97.4 ± 3.9</td>
<td>33.2 ± 1.7</td>
<td>34.2 ± 2.0</td>
<td>1.52 ± 0.35</td>
</tr>
<tr>
<td>(3) Newborn infants with 2–10% Hb Bart’s (21)</td>
<td>6.15 ± 0.87</td>
<td>17.9 ± 2.9</td>
<td>52.8 ± 7.6</td>
<td>86.8 ± 5.1</td>
<td>29.3 ± 2.4</td>
<td>33.8 ± 2.0</td>
<td>4.98 ± 1.72</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Hb Bart’s at birth (%)</th>
<th>α/non-α ratio at birth</th>
<th>α/β-ratio at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.7</td>
<td>0.90</td>
<td>0.60</td>
</tr>
<tr>
<td>2</td>
<td>6.9</td>
<td>0.92</td>
<td>0.70</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
<td>0.69</td>
<td>0.70</td>
</tr>
<tr>
<td>4*</td>
<td>2.5</td>
<td>0.86</td>
<td>0.86</td>
</tr>
<tr>
<td>5</td>
<td>2.3</td>
<td>1.04</td>
<td>0.80</td>
</tr>
</tbody>
</table>

*Significantly higher mean red cell (RBC) counts (p<0.05) and significantly lower mean Hb (p<0.01), haematocrit (Hct) (p<0.001), mean corpuscular volume (MCV) (p<0.001), and mean corpuscular haemoglobin (MCH) (p<0.001) values than normal controls (1).

Newborn infants with 1 to 2% Hb Bart’s had significantly lower mean Hb (p<0.01), Hct (p<0.01), MCV (p<0.001), and MCH (p<0.001) values than controls (table 1).

There was a significant difference in mean red cell counts, MCV, and MCH values between the 1 to 2% and 2 to 10% Hb Bart’s groups (table 1).

**GLOBIN CHAIN SYNTHESIS RATIOS AND Hb BART’S IN NEWBORN INFANTS**

The results of globin chain synthesis analysis are shown in table 2. The α/non-α (β+γ) globin chain synthesis ratios in infants with more than 2% Hb Bart’s were within the normal range in three cases and consistently reduced in two. As can be seen in table 2 even the infants with normal α/non-α-ratios at birth had reduced α/β-ratios at follow-up examination at 9 to 28 months.

**TABLE 2** Globin chain synthesis analysis at birth and at 9–28 months in infants with Hb Bart’s higher than 2%

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Hb Bart’s at birth (%)</th>
<th>α/non-α ratio at birth</th>
<th>α/β-ratio at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.7</td>
<td>0.90</td>
<td>0.60</td>
</tr>
<tr>
<td>2</td>
<td>6.9</td>
<td>0.92</td>
<td>0.70</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
<td>0.69</td>
<td>0.70</td>
</tr>
<tr>
<td>4*</td>
<td>2.5</td>
<td>0.86</td>
<td>0.86</td>
</tr>
<tr>
<td>5</td>
<td>2.3</td>
<td>1.04</td>
<td>0.80</td>
</tr>
</tbody>
</table>

*This subject at follow-up examination showed a high Hb Aβ level and therefore he is a double α/β-thalassaemia heterozygote.

**FOLLOW-UP OF INFANTS WITH Hb BART’S**

Cellulose acetate electrophoresis showed that none of the children with 2 to 10% Hb Bart’s at birth had any haemoglobin variant and in particular no Hb H or Hb Bart’s at the time of examination. Two monozygotic twin infants with about 25% Hb Bart’s at birth died in the first week of life. Two developed the classical clinical and haematological picture of Hb H disease and one was lost at follow-up. Examination of blood smears showed mild hypochromia, anisocytosis, and poikilocytosis in all children who had 2 to 10% Hb Bart’s, while the
TABLE 3 Red cell indices (mean ±1 SD) and statistical evaluation of children aged 9–28 months who had variable amounts of Hb Bart’s at birth

<table>
<thead>
<tr>
<th>Subjects (No of cases)</th>
<th>RBC (×10¹²/l)</th>
<th>Hb (g/dl)</th>
<th>Hct (%)</th>
<th>MCV (fl)</th>
<th>MCH (pg)</th>
<th>MCHC (%)</th>
<th>Hb A₂ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Children without Hb Bart’s at birth (19)</td>
<td>4.97 ± 0.39</td>
<td>12.7 ± 0.6</td>
<td>36.9 ± 2.0</td>
<td>75.0 ± 3.7</td>
<td>25.6 ± 1.7</td>
<td>34.3 ± 1.6</td>
<td>2.5 ± 0.4</td>
</tr>
<tr>
<td>(2) Children with 1–2% Hb Bart’s at birth (9)</td>
<td>5.41 ± 0.50</td>
<td>12.8 ± 0.6</td>
<td>38.9 ± 2.1</td>
<td>72.2 ± 3.3</td>
<td>23.9 ± 3.1</td>
<td>32.7 ± 1.3</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>(3) Children with 2–10% Hb Bart’s at birth (13)</td>
<td>5.60 ± 0.44</td>
<td>11.7 ± 0.4</td>
<td>35.7 ± 1.1</td>
<td>64.6 ± 4.4</td>
<td>21.2 ± 2.0</td>
<td>33.0 ± 1.2</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>Group 2 vs 1</td>
<td>p&lt;0.025</td>
<td>NS</td>
<td>&lt;0.025</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Group 3 vs 1</td>
<td>p&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.025</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Group 3 vs 2</td>
<td>p NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.025</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Group with 1 to 2% had normal smears. Serum iron levels were normal in all cases. Two subjects with 2% and 2.5% Hb Bart’s at birth, respectively, were found to have β-thalassaemia trait with high Hb A₂. Their α/β-globin chain synthesis ratios were 0.81 and 0.86, respectively.

Children who had 2 to 10% Hb Bart’s at birth showed significantly higher red cell counts (p<0.001) and significantly lower mean Hb (p<0.001), MCV (p<0.001), MCH (p<0.001), mean corpuscular haemoglobin concentration (MCHC) (p<0.025), and Hb A₂ (p<0.05) values than normal (table 3).

Apart from higher RBC counts (p<0.025), lower Hct (p<0.025), and MCHC (p<0.02) values, there was no significant difference in mean red cell indices values between children with zero and 1 to 2% Hb Bart’s at birth (table 3).

The results of globin chain synthesis analysis are shown in fig 3. Children with 2 to 10% Hb Bart’s at birth had α/β globin chain synthesis ratios in the range previously found in obligate α-thalassaemia 1 carriers in our population (one of the parents of Hb H disease patients). Meanwhile, those with 1 to 2% Hb Bart’s at birth had a normal α/β globin chain synthesis ratio (two cases), or a slightly reduced ratio within the range already found in obligate α-thalassaemia 2 carriers in our population (the haematologically normal parent of Hb H disease patients) (two cases).

FAMILY STUDIES

Fig 4 shows the results of haematological and globin chain synthesis analysis in both parents and children.

**FIG 3** α/β-globin chain synthesis ratios at follow-up examination (9–28 months) in subjects with varying levels of Hb Bart’s at birth.

**FIG 4** α-thalassaemia genotype assessment in subjects with varying levels of Hb Bart’s at birth and in their parents.
together with a suggested genotype assignment, assuming that Sardinians have a full complement of four \( \alpha \)-chain structural genes, and that \( \alpha \)-thalassaemia has a transmission pattern like that seen in Orientals.

In family 3 the father is normal and the mother is an \( \alpha \beta \) double heterozygote, as she has high Hb A2 levels and an \( \alpha / \beta \) ratio of 0.78. Her probable genotype is therefore \( \beta^A A / \beta^ {	ext{thal}} A \), \( - / \alpha \alpha \) or \( - / \alpha / \beta \), according to previous results found in two families with \( \alpha \beta \) interacting thalassaemia.\(^{19} \) The child, who had 2.52\% Hb Bart's at birth, is also an \( \alpha \beta \) double heterozygote with high Hb A2 levels and an \( \alpha / \beta \) ratio of 0.86. His genotype is probably similar to that of the mother.

**Discussion**

Our study shows that 12.9\% of southern Sardinian newborn infants have Hb Bart's levels of more than 1\%, the upper limit of the Caucasian population.\(^{20} \)

This could be the result of a genetically determined defect of \( \alpha \)-chain synthesis, that is \( \alpha \)-thalassaemia, as has been shown in Orientals,\(^{2} \) and more recently in Negroes,\(^{3-4} \) Arabians,\(^{5} \) and Yemenite Iraqi Jews,\(^{22} \) or of a developmental abnormality as suggested by Esan\(^{33} \) in Nigeria.

The results of follow-up examination clearly showed that Hb Bart's levels of more than 2\% in our population are indicative of \( \alpha \)-thalassaemia. Children with about 25\% Hb Bart's at birth developed Hb H disease and those with 2 to 10\% Hb Bart's showed haematological findings, such as microcytosis and reduced \( \alpha / \beta \) ratios, compatible with the \( \alpha \)-thalassaemia homozygous carrier state (\( \alpha \)-thal 1).

However, at follow-up examination, children in the 1 to 2\% Bart's group, may show evidence indicative of the silent \( \alpha \)-thalassaemia carrier state (\( \alpha \)-thal 2), that is, slightly reduced \( \alpha / \beta \) ratios with normal or slightly modified red cell indices, or a normal condition, that is, normal red cell indices and balanced \( \alpha / \beta \) globin chain synthesis ratios.

These results indicate that the group of Sardinian infants with Hb Bart's ranging from 1 to 2\% includes normal subjects and silent \( \alpha \)-thalassaemia carriers. Alternatively, our results can be explained by a relative insensitivity either of the method used for Hb Bart's quantification in the low range of values or of globin chain synthesis analysis.

At follow-up, two children with 2.0 and 2.5\% Hb Bart's proved to be double heterozygotes for \( \alpha \)-thalassaemia and \( \beta \)-thalassaemia genes. Their \( \alpha / \beta \) ratios were similar to those already seen by us in \( \alpha \)-thal 1/\( \beta \)-thal double heterozygotes.\(^{19} \)

Theoretically, if they are \( \alpha \)-thal 1 they should have higher Hb Bart's levels at birth. However, an \( \alpha \)-thal 1/\( \beta \)-thal trait combination is probably associated with a smaller number of \( \gamma \)-chains than \( \alpha \)-thal 1 alone.

In this survey, the incidence of Hb H disease in newborn infants was 1 in 573 live births.

The frequency of heterozygous \( \alpha \)-thalassaemia 1 calculated from this Hb Bart's survey is 5.6\%. It should be pointed out that this figure is in close agreement with the \( \alpha \)-thalassaemia carrier rate previously found in the same population in a mass screening programme directed at the adult population.\(^{9} \)

From our results it is impossible to calculate an incidence figure for the \( \alpha \)-thalassaemia silent carrier state, but it appears that it is much less than the incidence of heterozygous \( \alpha \)-thalassaemia.

In our population the absence of two clearly distinguishable groups of infants with low (1 to 2\%) and intermediate (2 to 10\%) Hb Bart's levels, as in Thailand,\(^{2} \) may be because of the heterogeneity of the \( \alpha \)-thalassaemia syndrome in Sardinia, assuming that the different genotypes may be associated with different but overlapping Hb Bart's levels at birth.

It has already been shown that in our population there is \( \alpha \)-thalassaemia resulting from deletion and non-deletion defects.\(^{15} \) Moreover since there is a \( \beta \)-thalassaemia carrier rate of 13\%, there are many possible combination defects: one, two, or three \( \alpha \)-chain gene deletion associated with heterozygous or homozygous \( \beta \)-thalassaemia, and non-deletion \( \alpha \)-thalassaemia associated with heterozygous or homozygous \( \beta \)-thalassaemia.

Genotype assessment carried out in a few families showed that infants with Hb Bart's levels higher than 2\% may have, as expected, one of the following genotypes: \( - / \alpha \alpha \) (homozygous \( \alpha \)-thal 2) as in family 2, or \( - / \alpha \alpha \) (\( \alpha \)-thal 1) as in family 3.

With such a high frequency of \( \alpha \)-thalassaemia, it remains to be elucidated why there is no hydrops fetalis in the Sardinian population. This may be explained by three different mechanisms.

1. The deletion defect could be more extensive including the \( \omega \)-gene and therefore the homozygous condition could be lethal in the early weeks of gestation.\(^{9} \)

2. There is a prevalence of the non-deletion defect, although preliminary results suggest that this is not the case.\(^{15} \)

3. \( \alpha \)-thalassaemia trait commonly results from homozygosity of the \( \alpha \)-thalassaemia 2 gene (\( - / - \alpha \)), as recently found in the American Black population.\(^{24} \)

There is some discordance in the results of \( \alpha / \alpha \) globin chain synthesis ratios at birth in \( \alpha \)-thalassaemia carriers (Hb Bart's > 2\%) belonging to
different ethnic groups. In Saudi Arabs there was a reduced α/non-α ratio, while in American Negroes the ratio was balanced.\(^3\)

In our population children with Hb Bart’s levels from 2 to 10% ascertained as α-thalassaemia heterozygotes at follow-up examination, may have normal or reduced α/non-α ratios at birth. So it can be concluded that globin chain synthesis analysis at birth is not a conclusive method for the identification of heterozygous α-thalassaemia in our population.

Both groups of children with 2 to 10% and 1 to 2% Hb Bart’s, respectively, showed thalassaemia-like red cell indices in the neonatal period, although this was less marked in the second group.

The presence of thalassaemia-like red cell indices in the 2 to 10% Hb Bart’s group is in agreement with the results of Friedman et al.\(^3\) From our results, however, it can be concluded that the silent carrier state also has phenotypic haematological manifestations. Eventually this information would be useful for planning a newborn α-thalassaemia screening programme.

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Requests for reprints to Professor Antonio Cao, Clinica Pediatrica II, Università degli Studi Cagliari, Via Porcelli 1, 09100 Cagliari, Sardinia, Italy.
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