\(\alpha\) Thalassemia and the Hematology of Homozygous Sickle Cell Disease in Childhood


\(\alpha\) Thalassemia modifies the hematologic expression of homozygous sickle cell (SS) disease, resulting in increased total hemoglobin and HbA2 and decreased HbF, mean cell volume, reticulocytes, irreversibly sickled cells, and bilirubin levels. The age at which these changes develop in children with SS disease is unknown. Ascertainment of globin gene status in a large representative sample of children with SS disease has afforded an opportunity to study the hematologic indices in nine children homozygous for \(\alpha\) thalassemia (two-gene group), 90 children heterozygous for \(\alpha\) thalassemia (three-gene group), and 167 children with a normal \(\alpha\) globin gene complement (four-gene group). The two-gene group had significantly lower mean cell volumes from birth, higher red cell counts from one month, lower reticulocytes from three months, and higher HbA2 levels from one year, compared with the four-gene group. Children with three genes had intermediate indices but resembled more closely the four-gene group. Differences in total hemoglobin or in fetal hemoglobin between the groups were not apparent by eight years of age. The most characteristic differences of the two-gene group were the raised proportional HbA2 level and low mean cell volume, the latter having some predictive value for \(\alpha\) thalassemia status at birth.

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From The Medical Research Council Laboratories, University of the West Indies, Kingston, Jamaica; and the MRC Molecular Haematology Unit, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, University of Oxford, England.


Address reprint requests to Dr Graham R Serjeant, The Medical Research Council Laboratories, University of the West Indies, Kingston 7, Jamaica.

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RESULTS

Fetal hemoglobin (HbF) fell sharply over the first six months and more gradually thereafter (Fig 1), there being no consistent differences between the different groups. HbA2 levels increased with age (Fig 2) and were consistently and significantly higher in the three-gene group and highest in the two-gene group, the difference between the two-gene and the four-gene groups being significant at the 0.1% level throughout.

Total hemoglobin levels fell rapidly over the first three months and more slowly thereafter (Fig 3), and no consistent differences occurred between the groups. Mean cell hemo-
globin concentration (MCHC) varied considerably, lowest values trending to occur in the two-gene group and highest values in the four-gene group, but the differences were not consistent or significant. Red cell counts fell sharply over the values in the four-gene group, but the differences were not group and highest values occurred in the four-gene group, gradually (Fig 5). Lowest values occurred in the two-gene and significantly $(P < 0.05)$ lower count did occur at age of one month and seven years, values were consistently intermediate but similar to those in the four-gene group. Mean cell volume (MCV) declined with age to six months and then rose gradually (Fig 5). Lowest values occurred in the two-gene group and highest values occurred in the four-gene group, the differences being consistent and significant $(P < 0.01)$ at birth and at all ages. A similar pattern was observed with mean cell hemoglobin.

Reticulocyte counts fell sharply from birth and increased steadily after one month to 36 months. Mean values were lower in the two-gene group as compared with the four-gene group at all ages although the difference was only intermittently significant. Values in the three-gene and four-gene groups were generally similar, although they tended to be lower in the four-gene group. Mean cell volume (MCV) declined with age to six months and then rose gradually (Fig 5). Lowest values occurred in the two-gene group and highest values occurred in the four-gene group, the differences being consistent and significant $(P < 0.01)$ at birth and at all ages. A similar pattern was observed with mean cell hemoglobin.

In view of the significant differences in MCV between the $\alpha$ globin genotypes at birth, the value of this index in predicting the $\alpha$ globin genotype was examined. The ranges of MCV at birth in the two-, three-, and four-gene groups were 79 to 95: $n = 4$, 89 to 115: $n = 21$, and 91 to 120: $n = 48$ respectively, indicating lower values in the two-gene group but almost identical distribution in the three- and four-gene groups. The 95th percentile (calculated from mean + 1.64 SD) of the two-gene group was 100 fl and the fifth percentile of the 3-gene group was 87 fl indicating a probability of 0.05 that an infant with an MCV of >100 fl would be, and a similar probability than an infant with an MCV of <87 fl would not be, homozygous for $\alpha$ thalassemia 2. Applying this to the 22 children of unknown $\alpha$ globin genotype in whom values for MCV were available at birth, levels exceeded 102 fl in 20 children and were 97 fl in the remaining two, indicating a low probability that any of these individuals were of the two-gene type.

**DISCUSSION**

These observations on the evolution of the hematological changes in SS disease according to $\alpha$ thalassemia status are based on substantial numbers of patients. The 266 children represented 85% of the entire group with SS disease diagnosed at birth and 97% of those surviving. Thirty-seven children died before suitable diagnostic procedures became available, but it is unlikely that this loss seriously biased the prevalence of $\alpha$ thalassemia genotypes since the observed relative proportions agree closely with that predicted from the gene frequency and with figures derived from an older Jamaican population.4 This loss of children with unknown $\alpha$ globin genotypes renders this data set unsuitable for analysis of survival, although it is adequate for observing the development of hematologic changes within the different subgroups.

Some of the hematologic characteristics of $\alpha$ thalassemia emerge early, significantly lower volumes for MCV and MCH being present at birth.1 In homozygotes, the red cell

**Table 1. Number of Patients Contributing to Data for Each Genotype at Different Ages**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Two-Gene</th>
<th>Three-Gene</th>
<th>Four-Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Total)</td>
<td>(9)</td>
<td>(90)</td>
<td>(167)</td>
</tr>
<tr>
<td>6 mo</td>
<td>4</td>
<td>66</td>
<td>113</td>
</tr>
<tr>
<td>1 yr</td>
<td>3</td>
<td>55</td>
<td>97</td>
</tr>
<tr>
<td>2 yr</td>
<td>6</td>
<td>67</td>
<td>127</td>
</tr>
<tr>
<td>3 yr</td>
<td>5</td>
<td>63</td>
<td>120</td>
</tr>
<tr>
<td>4 yr</td>
<td>8</td>
<td>65</td>
<td>128</td>
</tr>
<tr>
<td>5 yr</td>
<td>7</td>
<td>48</td>
<td>100</td>
</tr>
<tr>
<td>6 yr</td>
<td>7</td>
<td>41</td>
<td>90</td>
</tr>
<tr>
<td>7 yr</td>
<td>4</td>
<td>31</td>
<td>77</td>
</tr>
<tr>
<td>8 yr</td>
<td>5</td>
<td>27</td>
<td>67</td>
</tr>
</tbody>
</table>

![Fig 1. Fetal hemoglobin (mean ± 1 SD) as percentage of HbF from 0 to 6 months and as transformed values (log HbF + 4) from 1 to 8 years. $\alpha$ Globin genotypes: two-gene (■■■), three-gene (○—○), four-gene (□—□).](image)

![Fig 2. Hemoglobin $A_2$ percentage (mean ± 1 SD) from six months to eight years. Details as in Fig 1.](image)

![Fig 3. Total hemoglobin in grams per deciliter (mean ± 1 SD) from birth to eight years. Details as in Fig 1.](image)
of age. It is apparent therefore that most of the hematologic
differences characteristic of α thalassemia are apparent from
early in life.

Hematologic features in older populations with α thalas-
semia which have not yet emerged in the cohort study include
differences in MCHC, total hemoglobin, and HbF. There
was a consistent trend for lower values of MCHC to occur in
children with α thalassemia, but because of the variability of
values, this trend was not significant. No difference in total
hemoglobin levels was apparent by the age of eight years in
contrast to the consistently and significantly elevated levels
in α thalassemia in previous reports. This difference is
unexplained, although since values for MCHC and MCV
were still below levels for their respective genotypes in adults,
it is possible that the difference in total hemoglobin will
emerge as these indices stabilize in older children. Another
possible explanation is that in older patients the difference in
total hemoglobin levels was only significant between the
two-gene group and those with three or four genes. The
difference between levels in three- and four-gene groups in
that study was small and not significant, and the lack of
expected difference in the present study may be due to the
small numbers of patients in the two-gene group.

Data on HbF levels in older populations are conflicting. A
small study with five patients homozygous for α thalassemia
suggested a significant increase in HbF levels, and the
recent report from the American Cooperative Study showed
a slight but nonsignificant increase in the 13 patients with
homozygous α thalassemia diagnosed by gene mapping. In
contrast, a much larger Jamaican study of 44 patients with
homozygous α thalassemia, with carefully matched controls,
indicated significantly lower values. The magnitude of the
reduction was small and was postulated to result from
decreased F cell selection secondary to a lower hemolytic
rate. Because evidence from reticulocyte counts was consis-
tent with less hemolysis in the present study also, the reason
for a lack of difference in HbF by the age of six years is
unknown.

It appears that the effects of interacting α thalassemia are
generally identifiable within the first few months of life.
There is evidence for a reduced hemolytic rate with
decreased reticulocyte and increased red cell counts,
although no differences in total hemoglobin or HbF are
apparent by age eight years. The effect of reduced α globin
production is manifest by reduced MCV and MCHC, both of
which are theoretically likely to diminish intravascular sick-
ling. The overall pattern of the hematologic features seen in
Jamaican SS children with homozygous α thalassemia 2
appears similar to that in children with sickle cell β thalasse-
mia, whereas evidence from older patients suggests that
their clinical course is similar.

Clinical data derived from the α globin genotypes in the
Jamaican sickle cell cohort study is still at an early stage of
collection and analysis. The α globin genotype did not appear
to influence the age at which specific symptoms of the
disease developed and the effects of α thalassemia on
splenic complications are complex. There is a suggestion that
acute splenic sequestration may be less common in the
two-gene group, but preliminary unpublished observations
suggest that such patients may be more prone to hypersplen-
ism, consistent with observations in older patients. There is
doubt on the role of α thalassemia in survival in SS
disease; Mears et al noted a significant excess of three-gene
individuals in older patients, whereas Higgs et al were
unable to show an increasing prevalence of two-gene individ-
uals with age. These observations could be consistent if the
survival benefit of three-gene individuals was compromised
by the higher hemoglobin level or other features characteris-
tic of the two-gene group. Unfortunately, because of the
unknown α globin genotypes of many of the early deaths, the
cohort study cannot contribute to this controversy in relation
to early mortality.

REFERENCES

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Alpha thalassemia and the hematology of homozygous sickle cell disease in childhood

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