The First Observation of Homozygous Hemoglobin S-Alpha Thalassemia Disease and Two Types of Sickle Cell Thalassemia Disease: (a) Sickle Cell-Alpha Thalassemia Disease, (b) Sickle Cell-Beta Thalassemia Disease

By Muzaffer Aksoy

SICKLE CELL-THALASSEMA DISEASE is known to be a severe or moderately severe type of congenital hemolytic anemia. The clinical and hematologic pictures of this hemoglobinopathy are usually similar to those found in the intermediate type of Cooley's anemia; however, mild or asymptomatic cases have been reported by various investigators. Singer et al. have described four Negro patients with mild sickle-cell thalassemia disease. In one of the patients, all hematologic indices including the MCV were within normal limits. Aksoy and Lehmann and later Aksoy reported a total of 11 cases of sickle-cell-thalassemia disease among Eti-Turks. Also in this community, five individuals were discovered who were heterozygous for thalassemia and hemoglobin S genes and they were neither anemic nor symptomatic.

In sickle cell-thalassemia disease, the amount of hemoglobin S is highly variable, but it is usually more than 50 per cent. Silvestroni and his associates have reported that high values of hemoglobin S ranging between 67.9 and 97.1 per cent are constantly found in this hemoglobinopathy. Neel reported two families in which both genes appeared to be present and hemoglobin analyses revealed that the patients had low hemoglobin A fractions, 22.3 and 36.2 per cent respectively. Aksoy also noticed that in two of his patients the proportion of hemoglobin A was greater than that of hemoglobin S.

The genetic view postulating "the existence of more than one kind of gene capable of producing the stigmata of thalassemia" was first evolved by Zuelzer et al. This concept was based upon the extraordinary variability in the interaction of thalassemia and other hemoglobin genes and brought forth the probability of the existence of more than one thalassemia gene.

Recently, Ingram and Stretton postulated that the thalassemia gene is a product of mutation of either alpha or beta hemoglobin chains similar to that observed in the abnormal hemoglobins, but without effect on the electrophoretic behavior of the hemoglobin molecule. This genetic concept is the basis for the classification of thalassemia into two major forms, alpha and beta thalassemias. Beta-thalassemia would be accompanied by an elevation of...
hemoglobin A₂ and fetal hemoglobin fractions since it has been speculated that
extra delta or gamma chains would be produced to compensate for the slow rate
of synthesis of beta chains and, therefore, allelism or close linkage with genes
for hemoglobin S and hemoglobin C would be expected. Contrary to this,
alpha thalassemia would not be associated with increased hemoglobin A₂
or fetal hemoglobin since these require alpha-chains. Alpha thalassemia gives
rise to the formation of hemoglobin H or hemoglobin Bart's, which was made
up of four beta chains and four gamma chains respectively. Recently,
Zuelzer et al.⁵ have noted a reciprocal relationship between the levels of
fetal and A₂ hemoglobins in beta thalassemic heterozygotes.

Currently, it is generally accepted that one group of thalassemia alleles
is not allelic with those of hemoglobins S and C.¹⁰,¹¹ Therefore, it is theoretically possible for the gene for thalassemia to be present in a subject carry-
ing two genes for two different abnormal hemoglobins. For example, if a
person with sickle cell trait marries an individual with sickle cell-thalassemia
disease, there are six possibilities for their offspring: normal, sickle cell trait,
heterozygous thalassemia, homozygous sickle cell anemia, sickle cell-thalas-
semia disease, and homozygous hemoglobin-S-heterozygous thalassemia dis-
ease.

In the past few years we have observed seven patients with sickle cell-
thalassemia disease. Five of these patients have shown all of the clinical and
hematologic findings of a severe or moderately severe type of sickle cell-
thalassemia disease. One of these patients, an 18 year old girl from Siverek, a
small town in the Southeast part of Turkey, has shown all the stigmata of a
severe type of sickle cell-thalassemia disease (sickle cell-beta thalassemia
disease) and is not included in this series. In contrast to these cases, the other
two patients presented as examples of the mild or asymptomatic type of this
hemoglobinopathy (non-interacting type of sickle-cell thalassemia disease).
In addition to this, a considerable difference in the results of hemoglobin
analysis in these two types of sickle cell-thalassemia disease has been estab-
lished. During the study of one of these families, a case of homozygous
hemoglobin S-alpha thalassemia disease was found.

The purpose of this paper is to report the first case of homozygous hemoglo-
bin S-alpha thalassemia disease, to describe six patients with sickle cell-
thalassemia disease, and particularly to discuss several genetic concepts
which might explain the development of the thalassemia syndromes.

Materials and Methods

Routine hematologic examinations were carried out according to standard methods.
Alkali-resistant hemoglobin was determined by the method of Singer et al.¹² Hemoglobin
analyses were performed by paper and starch gel electrophoresis according to the method
of Simithies.¹³,¹⁴ We used hydrolyzed starch,⁶ borate buffer (0.022 M boric acid plus
0.0088 M sodium hydroxide), 19 mA of current, 190–210 volts for a duration of 12–18
hours. Hemoglobin A + E solutions were used as controls. The concentration of hemo-

*Connaught starch hydrolyzed for gel electrophoresis.
globin A2 in the eluate was determined in a Unicam spectrophotometer. All analyses were performed in triplicate. The values for hemoglobin A2 by this method are considered normal up to 5 per cent.

Six patients with sickle cell-thalassemia disease were investigated. Five of them were Turks and one was an Eti-Turk (Case 5). The clinical manifestations, hematologic data, the results of hemoglobin analyses and family studies are summarized in tables 1–4. One case of homozygous hemoglobin S-alpha thalassemia disease was investigated and studied in a similar manner.

Case Report (Propositus)

M. A., a 4½ year old Turkish boy from Antalya, a city on the Eastern Mediterranean, was admitted to the hospital because of anemia and lassitude. The patient had been normal until the age of 18 months when lassitude and irregular fever were first noted. Frequent episodes of epistaxis had occurred during the 18 months prior to admission, but there was no history of petechiae or ecchymoses. Scleral icterus was noted by the parents on several occasions during this time. Two months prior to admission, he developed arthralgia which persisted for 15 days.

Physical examination revealed a normally developed moderately pale white boy with mildly icteric sclerae. The spleen was palpated two fingerbreadths below the left costal margin; the remainder of the physical examination was negative. A bone survey revealed mild thickening of the cranial vault and a “honeycombed” appearance around the elbow joint.

Laboratory examinations revealed the following: Red blood cells, 2,900,000/cu. mm., hemoglobin 6.8 Gm. per cent, color index 0.8, hematocrit 22 per cent, MCV 75.8 cu. μ, MCH 23.4 gamma gamma, reticulocytes 13 per cent, platelets 75,000/cu. mm., white blood cells 18,500/cu. mm. with 32 per cent neutrophils, 3 per cent band forms, 2 per cent eosinophils and 63 per cent lymphocytes. There were seven nucleated red cells per 100 white blood cells. Marked anisocytosis, poikilocytosis and polychromasia were noted and the majority of the red blood cells were hypochromic and microcytic (fig. 1). There were several microelliptocytes, together with some sickle cells and target cells. Total bilirubin was 2.1 mg. per cent, serum iron 140 gamma per cent and osmotic fragility 0.40 – 0.20 per cent of sodium chloride. The bleeding time was 4 minutes. The clotting and the prothrombin times were within normal limits.

Hemoglobin analyses performed by paper and starch gel electrophoresis showed that the hemoglobin pattern was S + F (fig. 2). Alkali-resistant hemoglobin determined by the alkali denaturation method was 27 per cent. After elution from starch gel, hemoglobin S was found to be 70.5 per cent and the hemoglobin A2 fraction was 2.5 per cent. The sickling test was positive.

Hospital course: The patient was given five units of whole blood and then splenectomized with no postoperative complications. The spleen weighed 330 Gm. and the intrasplenic pressure was 70 mm. of saline. Microscopic examination of the spleen revealed evidence of generalized passive congestion of the sinusoids. Iron-staining pigment was not present in excessive amounts.

The hematologic data following splenectomy were as follows: red blood cells 3,900,000/cu. mm., hemoglobin 9 Gm. per cent, hematocrit 31 per cent, MCV 80 cu. μ, MCH 23 gamma gamma, reticulocytes 8.5 per cent, platelets 580,000/cu. mm., white blood count 6,500/cu. mm. with 38 per cent neutrophils, 3 per cent band forms, 3 per cent eosinophils, 5 per cent monocytes and 51 per cent lymphocytes. There was marked anisocytosis, poikilocytosis, polychromasia, microcytosis, several target cells and ovalocytes, and some sickle cells in the blood smear. The total bilirubin was 0.9 mg. per cent and the serum iron was 143 gamma per cent.

Family study (fig. 3): The patients' parents were of Turkish origin and first cousins. The father had sickle cell trait and the mother (Case 6) had asymptomatic sickle cell-
alpha thalassemia disease. The clinical manifestations, hematologic data, and results of hemoglobin analyses of the mother are summarized in tables 1–3. Samples of blood from the patient's sisters were sent to our laboratory and examined. One sister, S. A., a 16 year old girl, had sickle cell anemia and the hematologic data are summarized in table 4.

**DISCUSSION**

As can be seen from tables 1–4, Cases 1–4 are classic examples of a severe or moderately severe type of sickle cell-thalassemia disease. They exhibited all stigmata characteristic of this hemoglobinopathy, such as marked hepatosplenomegaly, the morphologic abnormalities, the corpuscular constants, the increased osmotic resistance of the erythrocytes, signs of increased hemolysis and hypochromic microcytic anemia (fig. 4). Hemoglobin analyses showed that the fraction of hemoglobin S was very high, 68.45, 74, 77.3 and 77.4 per cent respectively (table 3). On the other hand, the fraction of hemoglobin A was found to be in very small amounts, ranging between 1.5 and 6.34 per cent. These results are similar to those found by Silvestroni and his associates.\(^6\) The hemoglobin A\(_2\) fraction was found to be increased in these cases, ranging between 4.3\(\%\) and 7.3 per cent.

The genetic pattern of these patients was consistent with the diagnosis of sickle cell-thalassemia disease, i.e., one of the parents had sickle cell trait and the other exhibited all the stigmata of heterozygous thalassemia with an increased hemoglobin A\(_2\) fraction.

\(^{6}\)A fast-moving component of hemoglobin S, hemoglobin \(S_\alpha\), like those of some other abnormal hemoglobins, has been demonstrated.\(^{17}\) The relation of these abnormal hemoglobins to the major fraction, hemoglobin \(S_p\), is comparable with that of hemoglobin 3 to hemoglobin 1. Therefore, some parts of the small amount of hemoglobin A\(_2\) found in our patients might be due to this fast-moving component of hemoglobin S. Unfortunately, no attempt was made to eliminate this possibility.

\(1\)This result was obtained by Dr. E. Silvestroni and Dr. I. Bianco by the method of starch block electrophoresis.
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Fig. 2.—Starch gel electrophoresis at alkaline pH. From left to right: A + S + A₂ (sickle cell-alpha thalassemia disease: the mother); F + S + A₂ (sickle cell anemia: the sister S.A.); A + F + S + A₂ (homozygous hemoglobin S-alpha thalassemia disease: the propositus; the presence of Hb A is due to several blood transfusions); A + S + A₂ (sickle cell trait: the father). The gel was photographed after staining with Buffalo-black in methanol.

In one of the parents with thalassemia minor, the MCV was decreased, but in three of them the MCV was not below 82 cu. μ. As we have emphasized in another paper,¹⁵ we do not consider microcytosis as a unique feature of the heterozygous form of thalassemia disease. In a survey of family studies among thalassemic syndromes, we have observed several examples of thalassemic parents who did not show a decreased MCV.¹⁶

The elevated level of hemoglobin A₂ in these patients with sickle cell-thalassemia disease and in their parents indicates the presence of a thalassemia gene which is presumed to effect suppression of beta-chain synthesis (beta thalassemia).

In contrast to the above-described four patients, Cases 5 and 6 were nearly asymptomatic and the results of the hemoglobin analyses were entirely different. Clinical manifestations of Cases 5 and 6 were very mild. Case 5 complained only of arthralgia which started in childhood and resembled that seen in sickle cell anemia. She had mild splenomegaly and appeared to be somewhat infantile. Case 6 was entirely asymptomatic. Neither patient was severely anemic, but both had slightly reduced hemoglobin levels (11.2 and 13.3 Gm. per cent), and decreased MCV's (81 and 82.5 cu. μ). Both patients had mild to moderate morphologic abnormalities in the form of ovalocytosis, microcytosis (fig. 4) and decreased osmotic fragility. There was
no evidence of increased hemolysis. The results of the hemoglobin analyses differed from the results obtained in Cases 1–4 (fig. 5). In both patients, the level of hemoglobin S was less than the level of hemoglobin A, i.e., 41.9 and 46.5 per cent. Furthermore, hemoglobin F was absent and hemoglobin A₂ was within normal limits. The genetic study of Case 5 showed that the father had sickle cell trait and the mother had thalassemia minor. The mother had hematologic findings consistent with heterozygous thalassemia, i.e., reduced hemoglobin, decreased MCV, low MCH, microcytosis, leptocytosis and a normal serum iron; however, hemoglobins F and A₂ were within normal limits.

Unlike beta-thalassemia, the criteria for alpha chain thalassemia trait cannot be sharply defined. Despite this, considering the hematologic findings characteristic for heterozygous thalassemia with normal hemoglobin A₂ and hemoglobin F values, we are inclined to assume that the mother of Case 5 had possibly a thalassemia gene which presumably effected suppression of alpha-chain synthesis.

The results of the family study of Case 6 were of interest (fig. 3). She married a man with sickle cell trait; they had four children: one with sickle

Fig. 3.—Genealogy of a family with homozygous hemoglobin S-alpha thalassemia disease. (Numbers refer to the age of the subjects.)
cell trait, one with sickle cell anemia, one with homozygous hemoglobins S-alpha thalassemia disease; one of them was not examined.

As we have described above, these two types of sickle cell-thalassemia disease differ significantly. The differences include:

1. Clinical and hematologic picture: Cases 1–4 (beta-thalassemia) are severe enough to incapacitate them throughout their lives. On the other hand, Cases 5 and 6 (alpha-thalassemia) were almost asymptomatic.

2. Hemoglobin analyses: The hemoglobin pattern of Cases 1–4 is S + F ± A with an increased hemoglobin A2 fraction. The level of hemoglobin S is very high, between 68.45 and 77.4 per cent. Contrary to this, the hemoglobin pattern of Cases 5 and 6 is S + A with a normal hemoglobin A2 fraction; the level of hemoglobin S is less than hemoglobin A.

3. Genetic study: Although the genetic pattern was the same in both groups, the results of hemoglobin analyses obtained in the thalassemic parents were a little different. The thalassemic parents of Cases 1–4 had an increased hemoglobin A2 fraction (beta-thalassemia). Contrary to this, the thalassemic parent of Case 5 had normal hemoglobin A2 and hemoglobin F fractions (possibly alpha-thalassemia).

Ingram and Stretton9 propounded the “substitution hypothesis” to explain the highly variable proportion of hemoglobin S occurring in some of the patients with sickle cell-thalassemia disease. According to this hypothesis, both the thalassemia gene and the hemoglobin S gene affect beta-polypeptide chain synthesis. It might be expected, therefore, that the ratio of hemoglobin S to normal hemoglobin would be higher in sickle cell-thalassemia disease than in sickle cell trait. Contrary to this, if the thalassemia gene affects alpha polypeptide chains, the proportion of hemoglobin A would be expected to be higher than that of hemoglobin S.

On the basis of the hypothesis of Ingram and Stretton and the results of the hemoglobin analyses obtained in the patients with sickle cell-thalassemia...
Table 2.—Hematologic Data on Six Patients with Sickle Cell-Thalassemia Disease

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Hematologic Data 1</th>
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<th>4</th>
<th>5</th>
<th>6</th>
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<td></td>
<td>RBC (10⁶/cu.mm.)</td>
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<td>3.50</td>
<td>3.30</td>
<td>3.70</td>
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<td>Hb (Gm.%)</td>
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<td>8</td>
<td>7.6</td>
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<td>WBC/cu.mm.</td>
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<td>Reticulocytes (%)</td>
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<td>Hematocrit (%)</td>
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<td>38</td>
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<td>MCV (μπ)</td>
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<td>77</td>
<td>71</td>
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<td>MCH (γγ)</td>
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<td>22.5</td>
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<td>NRC/100 WBC</td>
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<td>++</td>
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<td></td>
<td>Microcytosis</td>
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<td>++</td>
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<td>Basophilic stippling</td>
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<td></td>
<td>Ovalocytosis</td>
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<td>++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
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<td></td>
<td>Sickle cells</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
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<td>Total bilirubin (mg.%</td>
<td>2.83</td>
<td>4.39</td>
<td>1.6</td>
<td>0.9</td>
<td>0.8</td>
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<td>Osmotic fragility (% NaCl)</td>
<td>.46–.16</td>
<td>.4–.18</td>
<td>.42–.16</td>
<td>.34–.20</td>
<td>.42–.24</td>
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<td>Serum iron (γ %)</td>
<td>166</td>
<td>112</td>
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<td>130</td>
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Table 3.—The Results of Hemoglobin Analysis in Six Patients with Sickle Cell-Thalassemia Disease

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Fetal Hb %</th>
<th>Hb A %</th>
<th>Hb A %</th>
<th>Hb S %</th>
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<td>1</td>
<td>16</td>
<td>5.2</td>
<td>1.5</td>
<td>77.3</td>
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<td>2*</td>
<td>11.96</td>
<td>4.3</td>
<td>6.34</td>
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<td>3</td>
<td>22.75</td>
<td>7.3</td>
<td>1.5</td>
<td>68.45</td>
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<td>4</td>
<td>13.8</td>
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<td>5</td>
<td>0</td>
<td>2.5</td>
<td>51.0</td>
<td>46.5</td>
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<tr>
<td>6</td>
<td>0</td>
<td>4.1</td>
<td>54.0</td>
<td>41.9</td>
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*These results were obtained by Dr. E. Silvestroni and Dr. I. Bianco by the method of starch block electrophoresis.

disease and those of their parents, we propose that Cases 1–4 have sickle cell-beta thalassemia disease and Cases 5 and 6 have sickle cell-alpha thalassemia disease. The above-mentioned differences in symptomatology and hematologic manifestations of our patients could be explained by the presence of different thalassemia genes in the respective cases.

**Homozygous Hemoglobin S-Alpha Thalassemia Disease**

A careful analysis of the hematologic findings and the genetic study obtained in the propositus brought about the possibility that the patient carried two genes for hemoglobin S and a gene for alpha thalassemia. The findings compatible with the possibility of this genetic anomaly may be classified into two groups:
A CASE OF HB S-ALPHA THALASSEMIA DISEASE

1. The presence of two genes for hemoglobin S in the propositus: The patient had an S + F hemoglobin pattern with a normal hemoglobin A2 value. The proportion of fetal hemoglobin was 27 per cent. These findings can only be consistent with the presence of two genes for hemoglobin S, heterozygosity for the hemoglobin S gene, as well as a high F hemoglobin gene, and double heterozygosity for hemoglobin S and thalassemia genes. If it is assumed that the patient is doubly heterozygous for hemoglobin S and a high F hemoglobin gene, a mild or normal clinical and hematologic picture would be expected. This was not the case, however. The severity of the clinical and hematologic picture of the propositus cannot be explained by the possibility of being doubly heterozygous for hemoglobin S and thalassemia genes. In that case, the child would have inherited the thalassemia gene from his mother and the sickle cell gene from either the father or the mother. As we have described above, the mother of the propositus was a case of asymptomatic sickle cell-alpha thalassemia disease (Case 6). Therefore, the child should have been entirely asymptomatic and his hemoglobin pattern should have been A + S, like his mother, but the severity of the disease in the propositus absolutely excluded this possibility. For this reason, we are inclined to assume that the child carried two genes for hemoglobin S.

2. The presence of one gene for thalassemia in the propositus: In sickle cell
<table>
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<tr>
<th>Subject</th>
<th>RBC 10^6/cu.mm.</th>
<th>Hb Gm. %</th>
<th>Hct %</th>
<th>MCV cu.μ</th>
<th>MCH γγ</th>
<th>Reticulocytes %</th>
<th>Osmotic Fractility % NaCl</th>
<th>Target-Sickling Cells</th>
<th>Hb Pattern</th>
<th>Hb F %</th>
<th>Hb A₂ %</th>
<th>Serum Iron γ %</th>
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<td></td>
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<tr>
<td>Mother</td>
<td>5.00</td>
<td>11.5</td>
<td>42</td>
<td>84</td>
<td>22.0</td>
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<tr>
<td>Father</td>
<td>5.10</td>
<td>14.0</td>
<td>47</td>
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<td>27.4</td>
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<tr>
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<td>Mother</td>
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<td>11.3</td>
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Table 4.—The Hematologic Data on the Family Members of Six Patients with Sickle Cell-Thalassemia Disease
anemia, the reduction in hemoglobin and in the volume of packed red cells is often proportional, unless there is a state of iron deficiency. The MCV is usually normal or, in the most anemic cases, above normal. The MCH, however, in sickle cell anemia is either normal or above normal, ranging between 32 and 36 gamma gamma. Contrary to this, the propositus had an MCV of 75.8 cu. μ, and an MCHC of 23.4 gamma gamma with a striking microcytosis and hypochromia in the blood smear. If it is assumed that the propositus is a case of sickle cell anemia complicated with iron deficiency, a low serum iron level should be expected. The presence of high serum iron level excluded this possibility. There are other theoretical possibilities for the hypochromia and microcytosis with high serum iron in the propositus, such as a pyridoxine-responsive anemia and some forms of "sideroblastic" refractory anemia. The absence of hemosiderosis in the spleen possibly excludes the assumption that the boy should have been a case of sickle cell anemia complicated with "sideroblastic" refractory anemia. The occurrence of pyridoxine-responsive anemia in man has been described by several authors. This anemia is hypochromic and microcytic with a high serum iron. Unfortunately, in this case no attempt was made to exclude this theoretical possibility.

The most probable explanation for the presence of microcytosis and hypochromia in the propositus is that he is also carrying one gene for thalassemia inherited from the mother. On the other hand, the difference in the hematologic picture of the propositus and the sister (S. A.) could be explained only
by the presence of the thalassemia gene in the former. In contrast to the hematologic findings of the propositus, the sister had a moderately severe normocytic and normochromic anemia (MCV 88.8 cu. µ, MCH 29.2 gamma gamma) with no microcytosis in the blood smear. Furthermore, the sister had an S + F hemoglobin pattern with a normal hemoglobin A2 fraction similar to those of the propositus. We can therefore assume that the sister is a case of sickle cell anemia who does not carry any thalassemia gene. The above-mentioned difference between the propositus and the sister who were both carrying two genes for hemoglobin S can be regarded as confirmatory evidence for the possibility that the former is also carrying one gene for thalassemia.

In regard to the thrombocytopenia in the propositus, this can be considered either as chronic idiopathic thrombocytopenic purpura which was benefited by splenectomy, or in some manner related to the disease, and more particularly to the splenomegaly.

**SUMMARY**

Six patients with sickle cell-thalassemia disease are reported together with hematologic and genetic data. A case of homozygous hemoglobin S-alpha thalassemia disease, the son of parents with asymptomatic sickle cell-thalassemia disease and sickle cell trait, is presented, showing the possibilities involved in the presence of two genes for hemoglobin S and one gene for thalassemia.

**SUMMARIO IN INTERLINGUA**

Es reportate le casos de sex patientes con thalassemia a cellulas falciforme, incluse datos hematologic e genetic. Es presentate un caso de homozigotic thalassemia a hemoglobina S alpha. Le patiente es le filio de parentes con asymptomatic thalassemia a cellulas falciforme e character de cellulas falciforme. Le caso illustra le possibilitates inherente in le presentia de duo genes pro hemoglobina S e un gen pro thalassemia.

**REFERENCES**

A CASE OF HB S-ALPHA THALASSEMIA DISEASE


Dozent Dr. Muzaffer Aksoy, 2nd Internal Clinic, Istanbul Medical School, Vakif Guraba Hospital, Capa-Istanbul, Turkey.
The First Observation of Homozygous Hemoglobin S-Alpha Thalassemia Disease and Two Types of Sickle Cell Thalassemia Disease: (a) Sickle Cell-A disoma (b) Sickle Cell-Beta Thalassemia Disease

MUZAFFER AKSOY