Sickle Cell–Thalassemia Disease in Jamaica

By J. E. MACIVER, L. N. WENT and E. K. CHUICKSHANK

SICKLE CELL—thalassemia disease was first reported by Silvestroni and Bianco in Italians in Europe.1–4 Cases have also been described in Italians and Greeks in the United States,4–8 in Negroes in Africa9 and the United States10–13 and in Eti-Turks.14 A recent paper describes 44 cases of the disease in Greece.3

Sickle cell—thalassemia disease results from the inheritance of two genes, the sickle cell gene and the thalassemia gene. These abnormal genes are thought to be nonallelomorphic. In the majority of reported cases one of them is inherited from each parent, but, exceptionally, both may be derived from the same parent,2 who then also has sickle cell—thalassemia disease.

In this disease production of normal hemoglobin is suppressed to a greater or lesser degree,7 so that the pattern found on electrophoresis of hemoglobin may closely resemble that seen in sickle cell anemia.11,14

The purpose of this paper is to report two examples of this condition in young women of mixed Chinese and African ancestry and to compare them with other cases which we have seen. To our knowledge the condition has not been previously reported in this racial mixture.

METHODS

Standard hematologic methods were used.15
In vitro sickling tests were carried out using 2 per cent sodium metabisulfite.16
Fetal hemoglobin was determined by the alkali denaturation technic described by Singer et al.17
Filter-paper electrophoresis of hemoglobin was performed in a horizontal tank using barbitone buffer of pH 8.6 and ionic strength about 0.02. The technic has been described by us elsewhere.18

Description of Findings

Case reports on two patients with the results of family studies follow. Hematologic data are summarized in table 1.

Case 1. Miss B.C., a 15-year-old girl of mixed African and Chinese extraction, was first seen in the University College Hospital in September 1953 at which time she complained of tiredness for one year. She had had frequent attacks of “malaria” as a child. In May 1953 she developed pains in the knees and ankles and a slight fever lasting a few days. She was jaundiced at that time. On examination there was pallor and icterus of her conjunctivae. The spleen was enlarged to five-finger breadths below the costal margin and was smooth, firm and nontender. No malarial parasites were found. Radiologic examination of the skull showed no abnormality. A diagnosis of sickle cell anemia was made.

She was seen again at the University College Hospital in December 1956. She said that since 1953 she had had attacks of joint pains predominantly in the wrists and elbows.
Table 1.—Hematologic Data on Cases 1 and 2 and Their Families

<table>
<thead>
<tr>
<th>Name</th>
<th>Hb, Gm./100 ml</th>
<th>R.B.C.</th>
<th>M.C.V.</th>
<th>M.C.H.</th>
<th>Red.</th>
<th>Stained Film</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.C. (case 1)</td>
<td>8.3</td>
<td>3.9</td>
<td>26</td>
<td>67</td>
<td>32</td>
<td>13.6</td>
</tr>
<tr>
<td></td>
<td>Father</td>
<td>11.2</td>
<td>5.7</td>
<td>39</td>
<td>68</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td>14.1</td>
<td>4.8</td>
<td>45</td>
<td>94</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Brother</td>
<td>15.3</td>
<td>5.2</td>
<td>49</td>
<td>94</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Sister</td>
<td>13.0</td>
<td>5.1</td>
<td>42</td>
<td>82</td>
<td>31</td>
</tr>
<tr>
<td>M.A. (case 2)</td>
<td>10.6</td>
<td>—</td>
<td>34</td>
<td>—</td>
<td>31</td>
<td>25.0</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td>15.1</td>
<td>—</td>
<td>46</td>
<td>—</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Brother</td>
<td>16.0</td>
<td>—</td>
<td>47</td>
<td>—</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Sister</td>
<td>14.2</td>
<td>—</td>
<td>44</td>
<td>—</td>
<td>32</td>
</tr>
<tr>
<td>Daughter</td>
<td>12.7</td>
<td>5.0</td>
<td>41</td>
<td>82</td>
<td>31</td>
<td>—</td>
</tr>
</tbody>
</table>

*Six nucleated red cells per 100 white cells.

at intervals of three months lasting for about a week. One of these was severe enough to require her admission to another hospital for seven days, when jaundice was again noted. She had developed a large ulcer on the right leg, which had taken many months to heal. Apart from some breathlessness, palpitation and intermittent ankle edema she remained well between attacks. Examination disclosed a plump, healthy looking girl of normal physical development and predominantly Chinese appearance (fig. 1). There was no gross pallor or jaundice of the conjunctivae. A large ulcer scar about 2 inches in diameter was found on the right leg. The spleen was enlarged three-finger breadths below the costal margin and the liver was not palpable. The heart was not enlarged clinically or radiologically and the blood pressure was normal. There were no other significant clinical findings. Since that time no new physical signs have developed, and apart from occasional pains in her limbs she has felt well.

Examination of the blood showed anemia, reticulocytosis, positive sickling test, and a very abnormal blood film (table 1). The osmotic fragility of her erythrocytes was greatly decreased (fig. 2). Electrophoresis of hemoglobin revealed a pattern identical to that seen in sickle cell anemia (fig. 3). Scanning of strips suggested that there was approximately 14 per cent of a non-S fraction, and alkali denaturation revealed 16 per cent of fetal hemoglobin. (In our experience repeated scanning of good paper strips gives results which are accurate to ±5 per cent.) These findings indicate that measurable amounts of hemoglobin A are not present in this patient’s blood.

A study of Miss B.C.’s family (fig. 1) was made. Her father, mother, brother and sister are all alive and well. There are no other children of the marriage. The father is Chinese and was born in Hong Kong. Examination of his blood (table 1) revealed slight anemia, a decreased osmotic fragility (fig. 2) and a blood film which was typical of thalassemia minor. The sickling test was negative, and electrophoresis (fig. 3) revealed Hb A only.

The mother appeared to be pure Negro, and examination of her blood showed that she had the sickle cell trait (table 1 and fig. 3).

The brother was hematologically normal, and no evidence of thalassemia could be demonstrated (table 1, fig. 2). Electrophoresis showed hemoglobin A only (fig. 3).

The sister was found to have the sickle cell trait (table 1, fig. 3).

Case 2. Mrs. M.A., a 28-year-old woman of mixed African and Chinese extraction, was first seen on November 8, 1956 complaining of fever and pains of three weeks duration in her thighs. She had had mumps, measles and chicken pox as a child, but was otherwise well until 17 years of age when she had pains in her wrists and forearms for three weeks. There was no fever or jaundice. In 1949, after a normal pregnancy, she had a severe post partum hemorrhage, but made an uneventful recovery. Thereafter, from 1949 to 1953,
Fig. 1.—Family of case 1, showing from left to right: patient, sister, father, brother and mother.

Fig. 2.—Osmotic fragility curves on family members of case 1.

she had bouts of intermittent fever lasting from one to two weeks about once a year, which were not associated with joint pains or jaundice. In 1953 she had fever from 101 F. to 105 F. for two weeks, associated with pains in her arms and thighs, and then developed swelling and redness of the right tibia. A tentative diagnosis of osteomyelitis was made, but radiological examination of the bones showed no abnormality. She remained well until April 1955 when she experienced severe chills, high fever, jaundice and vomiting for one week. There were no bone or joint pains. She was in the hospital for 30 days and was treated with blood transfusions, intravenous fluids and antibiotics. At that time she was told that she had sickle cell anemia. Since then she has tired easily, but otherwise was well until three weeks prior to her attendance at the University College Hospital. On examination, she was a slightly built woman, predominantly Chinese in appearance. There was some pallor of the mucous membranes, but no jaundice. The tip of the spleen was palpable and firm, and the liver edge was just felt. There was some pain on external rotation of the right hip, but the movements were full. No other
significant abnormality was demonstrable. She had no further symptoms up to the present time.

Examination of the blood revealed anemia, reticulocytosis, a positive sickling test, and a very abnormal blood film. Electrophoresis again showed a pattern identical to that seen in sickle cell anemia. The non-S fraction was much smaller than was found in case 1, making reliable scanning impossible. Alkali denaturation gave a value of 9 per cent fetal hemoglobin. Again we conclude that measurable amounts of hemoglobin A are not present.

A study of Mrs. M.A.’s family was undertaken.

The father is dead. However, he was Chinese, born in Hong Kong.

The mother is a Jamaican of mixed Caucasian and Negro descent. Examination of her
blood showed no abnormality apart from a positive sickling test (table 1). Electrophoresis gave an A + S pattern.

One sister was not available; a second sister was found to be normal (without evidence of thalassemia minor), and a brother had the sickle cell trait. The patient has a daughter, aged 7 years, who was also found to have the sickle cell trait. All the siblings are strikingly Chinese in appearance.

**Discussion**

Clinically, hematologically and electrophoretically both patients appeared to be suffering from sickle cell anemia. However, both fathers were Chinese, having been born in Hong Kong and later emigrating to Jamaica. To fulfill the accepted theories of inheritance in sickle cell anemia \(^{19-21}\) both parents should carry the abnormal gene for sickling, but we are not aware that this gene has ever been described in the Chinese. On the other hand, the thalassemia gene is common in Eastern races, and the father of case 1 undoubtedly has thalassemia minor. In case 2 the father is dead, and we were not able to demonstrate the thalassemia gene in any of the patient’s siblings. However, we feel that sickle cell–thalassemia disease is much more likely in this case than is sickle cell anemia. The chances of her father (who must have been Chinese from the physical appearance of the patient) having the sickle cell trait and marrying a girl with the sickle cell trait (found in 10.9 per cent of Jamaicans \(^{22}\) ) must be very remote. There is, thus, no doubt that case 1 suffers from sickle cell–thalassemia disease, and it is reasonably certain that case 2 has the same condition. In both instances we have, on electrophoresis, an S + F hemoglobin pattern, no hemoglobin A being demonstrable. In previously published reports of this disease, hemoglobin A production has been more or less suppressed at the expense of hemoglobin S. Some results are summarized in table 2, from which it will be seen that the

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>Hemoglobin Type (%) of total Hb.</th>
<th>A</th>
<th>S</th>
<th>F</th>
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<tr>
<td>Banks et al. (1952)(^{20})</td>
<td></td>
<td>--</td>
<td>83</td>
<td>--</td>
</tr>
<tr>
<td>Neel et al. (1953)(^{1})</td>
<td></td>
<td>20</td>
<td>61</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>84</td>
<td>5</td>
</tr>
<tr>
<td>Smith &amp; Conley (1954)(^{1})</td>
<td></td>
<td>12</td>
<td>80</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>80</td>
<td>8</td>
</tr>
<tr>
<td>Motulsky et al. (1954)(^{11})</td>
<td></td>
<td>17</td>
<td>82</td>
<td>1</td>
</tr>
<tr>
<td>Sturgeon et al. (1955)(^{8})</td>
<td></td>
<td>10</td>
<td>70</td>
<td>20</td>
</tr>
<tr>
<td>Singer et al. (1955)(^{11})</td>
<td></td>
<td>14.7</td>
<td>82.8</td>
<td>2.5</td>
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<td></td>
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<td>11.6</td>
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<td></td>
<td></td>
<td>21.2</td>
<td>77.2</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.2</td>
<td>74.5</td>
<td>11.3</td>
</tr>
<tr>
<td>Shields et al. (1956)(^{11})</td>
<td></td>
<td>6</td>
<td>90</td>
<td>4</td>
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<tr>
<td>Allison (1956)(^{8})</td>
<td></td>
<td>16</td>
<td>62</td>
<td>22</td>
</tr>
<tr>
<td>Aksoy and Lehmann (1957)(^{14})</td>
<td></td>
<td>14.1</td>
<td>80</td>
<td>5.9</td>
</tr>
<tr>
<td>MacIver et al. (1957)</td>
<td></td>
<td>25</td>
<td>73</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27</td>
<td>72</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>73</td>
<td>5</td>
</tr>
</tbody>
</table>
proportion of hemoglobin A found is usually below 25 per cent. Recently Neel, Zuelzer and Lehmann all reported examples of complete suppression of hemoglobin A in the phenotype in cases of sickle cell–thalassemia disease. Josephson also described a case in which 90 per cent hemoglobin S and 10 per cent hemoglobin F, only, were found. A case has even been reported in which only hemoglobin S was found. It appears that the degree to which hemoglobin A is suppressed in the phenotype in sickle cell–thalassemia disease may vary greatly. Whether this is due to varying penetrance of the thalassemia gene or to the existence of different types of thalassemia, occurring perhaps in different racial groups, is difficult to say. That such different types of thalassemia may, in fact, occur is suggested by our findings in the following cases:

1. We are reporting in another article our studies of three generations of a large family of African descent. Briefly, the patient, her brother and two of her children have an S + F pattern on hemoglobin electrophoresis with high levels of fetal hemoglobin (27, 24, 10 and 12 per cent respectively). The patient’s father has the sickle cell trait, while her mother, one of her brothers and one of her children, although completely normal clinically and hematologically, have high levels of fetal hemoglobin in their blood (24 per cent, 28 per cent, and 16 per cent respectively). This family seems to possess a type of abnormal gene which may well be different from the normal thalassemia gene. It resembles that described by Edington and Lehmann in two African families.

2. We have also studied three families of mixed African and Caucasian origin in each of which a case of sickle cell–thalassemia disease was found. The distribution of hemoglobins in these cases is included in table 2. They conform to the more usual pattern in this disease in that measurable quantities of hemoglobin A were found on hemoglobin electrophoresis.

We feel that our findings here in Jamaica support the view that the thalassemia gene may not be homogeneous and that there may in fact be several thalassemia-like genes.

The clinical severity of sickle cell–thalassemia disease may vary greatly from a relatively mild disorder on the one hand to a severe hemolytic anemia on the other. Moreover, the disease may not present until late childhood, or even later, as in our case 2. It may well be that some of the cases of sickle cell anemia reported in adults are in fact cases of sickle cell–thalassemia disease, in view of the similar patterns which may be found on electrophoresis. A diagnosis of sickle cell anemia in adults cannot be regarded as proven in the absence of family studies. Nevertheless, there is no doubt that sickle cell anemia can occur in adults. We have investigated three generations of a large Jamaican family in which three cases of true sickle cell anemia were found. One of these, a woman 30 years of age, has four healthy children.

**Summary**

Two cases of sickle cell–thalassemia disease are described in young women of mixed Chinese and African parentage. On hemoglobin electrophoresis, a complete suppression of hemoglobin A was found, giving a picture indistin-
SICKLE CELL—THALASSEMA DISEASE IN JAMAICA 365

guishable from that seen in sickle cell anemia. The findings in these two cases are contrasted with those in other examples of this disease which we have studied in Jamaica. The importance of these findings in relation to the diagnosis of sickle cell anemia is discussed.

SUMMARIO IN INTERLINGUA

Es describite duo casos de morbo drepanocytemic-thalassemic in juvene femininas de parentage sino-african mixte. Le studio electrophoretic del hemoglobin revelava le complete suppression de hemoglobina A, con le resultato de un configuration non distinguibile ab illo vidite in anemia drepanocytic. Le constatazioni in iste duo casos es contrastate con observationes in altere exemplos del mesme morbo studiate per nos in Jamaica. Le importanti de iste constatazioni in relation al diagnose de anemia drepanocytic es discutite.

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