Sickle Cell Disease in India

By R. N. SHUKLA, B. R. SOLANKI AND A. S. PARANDE

SICKLE CELL TRAIT has been reported in members of non-Negroid races and ethnic groups.\(^1\) Homozygocity of the sickle cell gene is considered to be the cause of sickle cell anemia and heterozygocity results in asymptomatic sicklemia.\(^7\) Occasionally, cases of sickle cell disease are encountered in which only one of the parents shows the sickle cell trait. In such instances the other parent usually shows the presence of a gene responsible for some other hematologic abnormality.\(^8\)

In India the presence of sickle cell trait in different foci (the Vedda tribes of the South,\(^1\) the tribes of Western India,\(^6\) and certain labor tribes drawn from Orissa working in the Assam tea gardens\(^5\)) has been reported. In the course of the last few months we have come across cases of sickle cell disease as well as the sickle cell trait in some families in Marathi—(an Indian dialect) speaking population mostly drawn from the low economic groups. This indicates the existence of another focus in this region of our country (Nagpur and surrounding districts). Other abnormal types of hemoglobins so far reported in India, are thalassemia and hemoglobins D and E.\(^9\)\(^11\) The possibilities of their existence in various combinations with the S-gene, resulting in different hemoglobinopathies, are potentially present.

This report deals with four cases of sickle cell anemia and one case of sickle cell-thalassemia which have been investigated in detail.

CLINICAL MATERIAL AND METHODS

In the course of studies of cases of chronic hemolytic anemia from the outpatient department of the Medical College Hospital in Nagpur, India, five cases showed sickle cell disease. They belonged to Mahar and Kothi communities and were residents of Nagpur and surrounding districts.

Standard methods were employed for routine hematologic and biochemical investigations.\(^12\) Blood for sickling was examined by wet-sealed preparation and by the sodium metabisulphite method of Daland and Castle. Differential hemoglobin analysis was done by the alkali denaturation technic and paper electrophoresis.\(^13\)\(^14\)

OBSERVATIONS

The clinical manifestations are summarized in table 1.

The age incidence ranged from 2 years, 6 months to 16 years. The outstanding complaints were generalized weakness, irregular fever, abdominal and joint pains and pallor. The histories of illness were of long duration. Cases 4 and 5 presented symptoms of acute illness with jaundice and crises.

From the Department of Pathology and Bacteriology, Medical College, Nagpur, India. The authors thank Drs. S. Vaishnav, B. J. Subedar, S. Mukerjee and Bhattacharya for their interest in aiding this study. They also thank Prof. J. B. Shrivastav and Dr. P. M. Bhandarkar, Dean, Medical College, Nagpur, for their kind permission to submit this report. Submitted Mar. 22, 1957; accepted for publication Jan. 15, 1958.

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TABLE 1.—Clinical Data and X-ray Findings in 5 Cases of Sickle Cell Disease

<table>
<thead>
<tr>
<th>Case No.</th>
<th>K.N. Nagpur</th>
<th>W.K. Chanda</th>
<th>S.R. Betul</th>
<th>G.M. Nagpur</th>
<th>P.R. Nagpur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in Years</td>
<td>13</td>
<td>15</td>
<td>16</td>
<td>2½ yrs.</td>
<td>4</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Caste</td>
<td>Mahar</td>
<td>Mahar</td>
<td>Kosthi</td>
<td>Mahar</td>
<td>Mahar</td>
</tr>
<tr>
<td>Fever</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Lassitude</td>
<td>++</td>
<td>±+</td>
<td>++</td>
<td>±</td>
<td>+++</td>
</tr>
<tr>
<td>Abdominal Pains</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Swelling of Joints</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pain in Bones</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Jaundice</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Changes in Bones X-ray</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tendency to Ulcerations of Legs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Case 4 died in the hospital while under treatment. Splenomegaly was present in all the cases. None of the patients showed leg ulceration.

Hematologic findings are summarized in table 2. Values ranged as follows: Total R.B.C. were from 1.9 to 2.8 mill./cu. mm. Hemoglobin was from 4.5 to 7.6 Gm./100 cc. Hematocrit was from 17 to 28 per cent. MCV varied from 60 to 170 cu. μ and MCHC from 24 to 29 per cent. Reticulocytes were from 8 to 16 per cent and total white blood cells were from 8500 to 16,600/cu. mm. Peripheral smear showed anisocytosis, poikilocytosis and polychromatophilia; microcytosis was seen in case 5. Percentage of target cell and sickle cells varied from 6 to 35 and 1 to 8 respectively. Normoblasts were seen in all except case 2. Sickling was positive in all patients. Osmotic fragility was decreased (normal from 0.48 to 0.32 per cent NaCl), varying from 0.45 to 0.22 per cent NaCl.

Hemoglobin analysis, repeated several times, showed classical pattern of sickle cell anemia (cases 1 to 4) and SA or SA F pattern in case 5 (fig. 1). Alkali-resistant hemoglobin varied from 5.2 to 21 per cent (in our laboratory, normal control showed 2 per cent resistant pigment).

Family studies. The members of the families of these cases were studied as far as possible hematologically with a view to find out the gene relationship.

Case 1, K.N., 13 years old, from Nagpur, Mahar by caste. The following members of his family could be traced and examined. Father was dead. Mother, 28 years old, grandmother (paternal), 60 years old, and father’s sister, 45 years old are alive, healthy, and showed presence of sickle cell trait. A younger brother of the patient died at the age of two, but the cause of death could not be ascertained.

Case 2, W.K., 15 years old, from Chanda (a district bordering Nagpur), Mahar by caste. Both the parents are healthy and showed presence of sickle cell trait. Two younger brothers and one elder sister of the patient are alive but could not be examined.
Table 2—Hematologic and Biochemical Data

<table>
<thead>
<tr>
<th>Case No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R.B.C. 10^6 cu.mm.</td>
<td>2.5</td>
<td>2</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Hb. in Gm./100 cc.</td>
<td>7.5</td>
<td>4.8</td>
<td>7.6</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Hematocrit %</td>
<td>28</td>
<td>20</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>M.C.V. (cu.μ)</td>
<td>104</td>
<td>100</td>
<td>107</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>M.C. Hb. (γγ)</td>
<td>30</td>
<td>24</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>M.C.H.C. (%)</td>
<td>28</td>
<td>24</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Reticulocyte (%)</td>
<td>14</td>
<td>8</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>V.B.C. /cu.mm.</td>
<td>16,600</td>
<td>8,500</td>
<td>10,100</td>
<td>9,800</td>
</tr>
<tr>
<td></td>
<td>Poly. Neutrophils %</td>
<td>31</td>
<td>50</td>
<td>68</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Lymphocyte %</td>
<td>55</td>
<td>38</td>
<td>23</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Eosinophil %</td>
<td>10</td>
<td>8</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Basophil %</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Monocytes %</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Normoblasts/100 W.B.C.</td>
<td>2</td>
<td>—</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Anisocytosis</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Poikilocytosis</td>
<td>++++</td>
<td>+</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Polychromatophilia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Target Cells (%)</td>
<td>9</td>
<td>6</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Sickle Cells (%)</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Osmotic fragility</td>
<td>0.45-0.3</td>
<td>0.4-0.3</td>
<td>0.4-0.3</td>
<td>0.4-0.25</td>
</tr>
<tr>
<td></td>
<td>Serum Bilirubin in mg.</td>
<td>2.6</td>
<td>2.2</td>
<td>1.75</td>
<td>1.25</td>
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<tr>
<td></td>
<td>Vendenberg Reaction</td>
<td>Indirect</td>
<td>Delayed</td>
<td>Indirect</td>
<td>Indirect</td>
</tr>
<tr>
<td></td>
<td>Serum Proteins Total</td>
<td>4.9</td>
<td>3.8</td>
<td>4.1</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>Alb.</td>
<td>3</td>
<td>2.4</td>
<td>3.1</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>Globu.</td>
<td>1.9</td>
<td>1.4</td>
<td>1.0</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Urine Urobilinogen</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Alkali-Resistant Pigment %</td>
<td>7.4</td>
<td>5.2</td>
<td>8</td>
<td>21</td>
</tr>
</tbody>
</table>

Case 3, S.R., 16 years old, from Betul (a district bordering Nagpur), Kosthi by caste. Total family constituted of eight members. The mother of the patient, 45 years old, four brothers and one sister are alive; father was dead. Mother is healthy and showed presence of sickle cell trait. Out of four brothers one only did not show presence of sickle cell trait; sister could not be examined.

Case 4, G.M., 2 years and 6 months old, from Nagpur, Mahar by caste. The family consisted of only the parents and the patient. The earlier two siblings were dead. The parents, 35 and 29 years old, respectively, showed presence of sickle cell trait.

Case 5, P.R., 4 years old, Mahar by caste, from Nagpur. Mother, 25 years old, showed the presence of sickle cell trait. Father, 32 years old, is healthy and did not show sickling. A full hematologic investigation of the father's blood was done. The peripheral smear showed occasional target cells and leptocytes (2 to 3 per cent). Total Hb. was 12.6 Gm./100 cc. R.B.C. were 5.2 mill./cu. mm., PCV was 42 per cent, MCV was 80 cu. μ and MCHC, 30 per cent. Paper electrophoresis showed presence of adult hemoglobin only. Alkali-resistant fraction was 2 per cent.
DISCUSSION

In all these cases there was a history of antecedent anemia, jaundice, and episodes of bone, joint and abdominal pains characteristic of crises. They came from poorer communities and symptoms related to malnutrition were mostly intermingled with anemia. The growth was stunted in proportion to their age. Their features showed facies with prominent frontal bosses and cheek bones. Splenomegaly was a distinctive feature in all these patients. Malaria is endemic in these areas but it was ruled out by repeated peripheral blood examination for the presence of parasites. Much of the literature on

Fig. 1.—Paper electrophoretic pattern.

Fig. 2.—Genetic study of cases.
the positive survival value of the trait in a hyperendemic malarial area is
contradictory and confusing. These results are as yet inconclusive and
further work will be required in this region. In the case of sickle cell anemia
it has been postulated that malarial infection precipitates crisis. The
previous history of fever, bouts of crises and splenomegaly may be due to ante-
cedent malarial infection which was difficult to rule out except at the time
of investigation of the patients. Marked splenomegaly, a characteristic fea-
ture in our series, may be due to previous malarial infection in addition to
reticuloendothelial hyperplasia secondary to increased red cell destruction.
Hematologic findings of these cases agree closely with those of hemolytic
anemia. Morphologically, the smear presented a uniform picture except in
case 5 where the percentage of target cells and sickle cells was higher.
Increased erythopoiesis and hemolysis was evident by hematologic and bio-
chemical investigations. The type of anemia found in cases 1 to 4 was
macrocytic hypochromic and in case 5, microcytic hypochromic. Homozy-
gocity for the "S" gene could be established only in cases 2 and 4. In cases 1 and
3 proof was only indirect, since both respective fathers were dead. In case 1,
the sister and the mother of the deceased father showed sickle cell trait, and it
is presumed, therefore, that the father also was a carrier of the "S" gene.
Case 3 is more doubtful, but the presence of the sickle cell trait in most of
the family members suggests that the dead parent may also have been a
carrier. These considerations, therefore, tend to confirm the diagnosis of
sickle cell anemia in most of the first four patients. The blood picture of the father
of case 5 who failed to demonstrate sicklemia seems to be that of thalassemia
minor. This patient may therefore be heterozygous for the sickle cell and
thalassemia genes. Our cases, thus, fall into two groups, (a) sickle cell anemia,
and (b) sickle cell thalassemia.

It must be emphasized that reports of sickle cell anemia in India are rare.
This is because there has been a lack of awareness of the disease entity in
these regions, together with the difficulty in making a rapid and certain
diagnosis, especially in view of other forms of anemia which occur so com-
monly here. The possibility of existence of sickle cell anemia seems to be
greater than has been suspected hitherto.

The cases which we discovered belonged to Mahar and Kosthi communi-
ties. The Mahars are the "schedule-castes" of Maharashtra. They extend from
the Arabian sea coast to the jungles of Raipur and Bastar. It is a mixed com-
unity ranging in skin color from very fair to dark, and they cannot be
easily distinguished from other communities. The Kosthis are residents of
Nagpur and adjoining areas and are skilled weavers. They are well built,
of medium height, dark in color and comparatively big-headed. Their real
origin is not known. According to anthropological studies, Mahars occupy a
position midway between Marathas and the primitives. In the ancient past
there may have been a possible admixture of Veddian tribes and primitives
of the Eastern region, the primitives entering through the eastern gaps of
Chhatisgarh into Narbada and Tapti Valley and the Veddian advancing from
the South, thus producing a middle race of the above community. (See map,
fig. 3.)
The presence of sickle cell gene in this focus near Nagpur has significance in that the cases reported above belong to the present days' schedule caste and other communities and not to the aboriginal tribes (which have so far shown a high frequency of sickle cell gene in India). A subsequent survey at Nagpur has revealed 22.2 per cent of sickle cell trait in the Mahar community.

Summary

Five cases of sickle cell disease are reported with complete clinical, hematologic and genetic studies. Four were cases of sickle cell anemia and one had sickle cell thalassemia. The importance of the presence of a focus of sickling in this area has been discussed.

Summary in Interlingua

Cinque casos de morbo a cellulas falciforme es reportate con complete studios clinic, hematologic, e genetic. Quatro esseva casos de anemia a cellulas falciforme, in le quinte il se tractava de thalassemia a cellulas falciforme. Es discutite le importantia del presentia de un foco de falciformation in iste area.

References

8. ——, Itano, H. A. and Lawrence, J. S.: Two cases of sickle cell disease presumably due to the combination of the genes for thalassemia and sickle cell hemoglobin. Blood 8:434, 1953.
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