Thrombocytopenia and Congenital Syphilis in South African Bantu Infants

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The causes of thrombocytopenia in the newborn and young infant differ from those of older children and adults. Maternal antibodies, platelet sequestration during haemolytic disease of the newborn, and thrombocytopenia following replacement transfusion with stored blood, bacterial septicemia, and spirochaetal and protozoal infections are important causes of neonatal thrombocytopenic purpura. It may be a feature of the congenital aplastic anaemia associated with certain anomalies of bone, while in a proportion of cases the aetiology remains obscure.

Syphilis as a cause of neonatal thrombocytopenia has not been emphasized and is either not mentioned in standard works of haematology (Britton, 1963; Wintrobe, 1961) or is cited as a rare association (Mandel, 1962).

Our interest in the problem was first aroused by 2 cases of congenital syphilis associated with bleeding, thrombocytopenia, and anaemia. Although congenital syphilis is seen fairly frequently at Baragwanath Hospital, it was our impression that thrombocytopenia was rarely associated with this disease. A study was undertaken to assess the incidence of thrombocytopenia in syphilis, and to clarify the importance of syphilis as a cause of bleeding in newborn and young infants.

Material and Methods

A prospective investigation for thrombocytopenia was carried out in all cases of congenital syphilis presenting with anaemia, purpura, or bleeding, seen over a period of 18 months. The criteria for the diagnosis of congenital syphilis were clinical features consistent with syphilis and positive serology in either the mother or the child. Serological tests for syphilis in infants under the age of 6 months are considered unreliable, as there may be a passive transfer of antibodies to the foetal circulation, or a failure of the infant to develop antibodies in early infancy. Therefore, wherever possible, the maternal blood was studied.

Laboratory investigations on samples of venous blood included haemoglobin estimations, reticulocyte counts, and platelet enumeration by the direct method (Dacie, 1956). A platelet count of less than 100,000/c.mm. was considered abnormal. Red cell, white cell, and platelet morphology in the peripheral blood and bone-marrow were studied on films stained with Wright's stain. The Venereal Disease Reference Laboratory (VDRL) flocculation test for syphilis was performed by the technique described by Shaffer and Goldin (1962).

Bilirubin concentration was measured by the method of Lathe and Ruthven (1958). Blood cultures, toxoplasma complement-fixation and dye tests, and urine examination for cytomegalic virus were carried out in all cases.

Results

Over a period of 18 months congenital syphilis was diagnosed in 46 infants. Of these, 13 babies under the age of 3 months were found to have thrombocytopenia. During the same period, thrombocytopenia, unassociated with syphilis, was found in 9 infants in the same age-group. Platelet antibodies were thought to be responsible in 2 of them. 2 children had salmonella septicemia, and in yet another child, the thrombocytopenia was associated with bilateral renal vein thrombosis and uraemia. In 3 infants, the cause of the thrombocytopenia was obscure, and the ninth child died before being adequately investigated.

Case Reports

The following are detailed case descriptions of the first two infants studied in this series and are fairly typical (Tables I and II).

Case 12. This premature first-born infant was admitted at the age of 6 weeks weighing 4½ lb. (2-20 kg.). He had failed to thrive despite adequate breast-feeding. Malena was present, and the infant was found to be severely anaemic. Hepatosplenomegaly and an exfoliative rash of the palms and soles were present. The
haemoglobin level was 3·4 g./100 ml., and platelets were reduced to 32,000/c.mm. The VDRL test was positive in both the mother and the child, and radiological examination of the long bones showed the typical features of congenital syphilis. A blood transfusion and a course of penicillin brought about a clinical and haematological response.

Case 14. The second child of a mother with a normal obstetrical history, he was a full-term infant who had thrived well until shortly before admission. At the age of 6 weeks he became jaundiced and developed convulsions. Examination showed a child with 'snuffles', nasal bleeding, mild jaundice, and moderate pallor. The liver and spleen were both enlarged and a scrotal rash was noted. Shortly after admission, oedema of the lower extremities developed. The haemoglobin level was 5·4 g./100 ml. and platelets were reduced to 25,000/c.mm. The serum bilirubin was 2·6 mg./100 ml. with a direct fraction of 2·4 mg./100 ml. There was an albuminuria, and microscopical haematuria was noted. The CSF was normal. Radiological examination of the long bones showed the osseous changes of congenital syphilis, and the VDRL test was positive in both mother and child.

Table I summarizes the clinical features of the 15 cases of thrombocytopenia associated with congenital syphilis. The ages ranged from 1 to 80 days. A low birth weight was found in 9 babies, of whom 2, aged 6 weeks, had failed to thrive. Bleeding and gross anaemia were features in 10 cases and purpura was present in 4 of these. Those patients who did not show overt haemorrhage had petechiae with the exception of one (Case 15, Tables I and II), where thrombocytopenia was found on routine examination into the cause of an anaemia. The liver or the spleen or both these organs were enlarged in all cases. Typical skin rashes were present in 11 and

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**Table Clinical**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (days)</th>
<th>Weight (kg.)</th>
<th>Pallor</th>
<th>Bleeding</th>
<th>Purpura</th>
<th>Liver (Finger-breadths)</th>
<th>Spleen (Finger-breadths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>3·77</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2·35</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1·86</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1·41</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>2·00</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>2·86</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>2·72</td>
<td>+</td>
<td>Brusing</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>Prem.</td>
<td>+</td>
<td>Nose, pulmonary*</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>1·86</td>
<td>+</td>
<td>Nose</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>2·72</td>
<td>+</td>
<td>Nose, peritoneal*</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>33</td>
<td>3·95</td>
<td>+</td>
<td>Peritoneal</td>
<td>–</td>
<td>2</td>
<td>1 1/2</td>
</tr>
<tr>
<td>12</td>
<td>42</td>
<td>2·2</td>
<td>+</td>
<td>Melaena</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>42</td>
<td>1·72</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>46</td>
<td>4·22</td>
<td>+</td>
<td>Nose and mouth</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>80</td>
<td>5·94</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>1 1/2</td>
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</tbody>
</table>

* Necropsy finding.

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**Table Investigations of Blood, Bone-marrow**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (days)</th>
<th>Haemoglobin (g./100 ml.)</th>
<th>Leucocytes (per c.mm.)</th>
<th>Platelets (per c.mm.)</th>
<th>Reticulocytes (%)</th>
<th>Normoblasts/100 WBC</th>
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<tr>
<td>1</td>
<td>1</td>
<td>16·5</td>
<td>24,200</td>
<td>45,000</td>
<td></td>
<td>75/100</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>14·6</td>
<td>13,500</td>
<td>20,000</td>
<td>19</td>
<td>21/100</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>12·1</td>
<td>30,000</td>
<td>60,000</td>
<td>11</td>
<td>125/100</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>13·1</td>
<td>16,700</td>
<td>35,000</td>
<td>7</td>
<td>40/100</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>13·9</td>
<td>28,000</td>
<td>20,000</td>
<td>11</td>
<td>15/100</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>12·8</td>
<td>28,000</td>
<td>100,000</td>
<td>7</td>
<td>27/100</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>13·0</td>
<td>31,000</td>
<td>60,000</td>
<td>11</td>
<td>17/100</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>10·3</td>
<td>11,700</td>
<td>25,000</td>
<td>7</td>
<td>300/100</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>3·8</td>
<td>46,000</td>
<td>36,000</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>6·6</td>
<td>18,000</td>
<td>40,000</td>
<td>12</td>
<td></td>
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<td>33</td>
<td>4·9</td>
<td>25,800</td>
<td>35,000</td>
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</tr>
<tr>
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<td>42</td>
<td>3·4</td>
<td>36,700</td>
<td>32,000</td>
<td>5</td>
<td>10/100</td>
</tr>
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<td>42</td>
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<td>25,000</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>46</td>
<td>5·4</td>
<td>64,000</td>
<td>45,000</td>
<td>8·2</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>80</td>
<td>7·2</td>
<td>12,000</td>
<td>45,000</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
Thrombocytopenia and Congenital Syphilis in South African Bantu Infants

I Features

<table>
<thead>
<tr>
<th>Rash</th>
<th>Bone Changes on Radiograph</th>
<th>Other Features</th>
<th>Flocculation Test</th>
<th>Alive</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peeling palms and soles</td>
<td>+</td>
<td>Jaundice, raised direct bilirubin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Copper-coloured</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peeling palms and soles</td>
<td>-</td>
<td>Jaundice</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Peeling palms and soles</td>
<td>+</td>
<td>Jaundice, raised direct bilirubin, hydrocephalus</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Peeling palms and soles</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Peeling palms and soles</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Copper, on scrotum</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

The results of haematological investigations and other relevant data are summarized in Table II. All 15 infants were anaemic according to the average haemoglobin level quoted for normals in the various age-groups (Smith, 1960). The haemoglobin levels ranged from 3.4 to 10.3 g./100 ml. in infants over the age of 1 week and from 12.1 to 16.5 g./100 ml. in the remaining infants in whom haemoglobin estimations were carried out on the first day of life. The reduction in haemoglobin was accompanied either by a reticulocytosis ranging from 5 to 19% in 8 infants or by poikilocytosis and anisocytosis. After taking into account the normal range of white cells for the age, 11 showed a leukaemoid reaction. Counts ranged from 9,000 to 64,000/c.mm. Immature white cells and occasionally blast cells were prominent in the peripheral blood films, especially when the white cell count was high. Blood films of 12 infants showed scanty platelets. Platelet counts were reduced to below 50,000/c.mm. in 11, and ranged between 50,000 and 100,000/c.mm. in 3 infants. In one infant a platelet count was not done (Case 13).

Bone-marrow aspirates were studied in 8; of these 4 showed an amegakaryocytic picture, 3 the presence of scanty non-budding megakaryocytes, and 1 showed many non-budding megakaryocytes. The other bone-marrow elements were normal, except in

<table>
<thead>
<tr>
<th>Smears</th>
<th>Bone-marrow</th>
<th>Liver Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>Polychromasia</td>
<td>Megakaryocytes</td>
</tr>
<tr>
<td>Scanty</td>
<td>-</td>
<td>Average</td>
</tr>
<tr>
<td>Scanty</td>
<td>+</td>
<td>Average</td>
</tr>
<tr>
<td>Scanty</td>
<td>+</td>
<td>Average</td>
</tr>
<tr>
<td>Scanty</td>
<td>+</td>
<td>Average</td>
</tr>
<tr>
<td>Scanty</td>
<td>+</td>
<td>Average</td>
</tr>
<tr>
<td>Scanty</td>
<td>+</td>
<td>Average (bud-ving defect)</td>
</tr>
<tr>
<td>Scanty</td>
<td>-</td>
<td>Erythroid depression</td>
</tr>
<tr>
<td>Scanty</td>
<td>+</td>
<td>Average</td>
</tr>
<tr>
<td>Scanty</td>
<td>+</td>
<td>Average</td>
</tr>
<tr>
<td>Scanty</td>
<td>-</td>
<td>—</td>
</tr>
</tbody>
</table>

II and Liver Histology

consisted either of marked peeling of the palms and soles, or copper-coloured cutaneous plaques or circinate lesions. Radiographs showed periostitis and metaphysitis of the long bones in 6 of 7 children in whom this examination was carried out. Jaundice was observed in 6 children. The VDRL test was positive in all the mothers tested (13) and in all the infants tested (9).
the last-mentioned case (Case 11), where there was
a maturation arrest of the megakaryocytes and
erthroid hypoplasia. Of the 6 infants with icterus,
one died before appropriate investigations could be
done. The 5 survivors showed biochemical changes
compatible with hepatocellular damage, with
increase of both the direct and indirect fractions of
the serum bilirubin. Histological examination of
the liver in 3 cases showed increased extramedullary
haemopoiesis for the age of the patient.

Special staining techniques failed to demonstrate
spirochaetes in the organs of 3 patients who died.
The results of blood cultures and tests for toxoplasmosis and
cytomegalo inclusion body disease were
negative in all cases.

Discussion

The association of syphilis with thrombocytopenia
had not been noted before at Baragwanath Hospital,
yet from our study we have concluded that syphilis
is a most important cause of thrombocytopenia in
the first three months of life among African infants
admitted to this hospital. Clearly, awareness of
this condition has led to a marked increase in the
number of cases diagnosed.

The most recent case reports of congenital
syphilis and thrombocytopenia appeared in 1936,
when Josephs, reviewing anaemia of infancy,
described 2 children with congenital syphilis, in
whom thrombocytopenia and neutropenia were
associated with a marked erythroblastosis and
lymphocytosis. Necropsy showed replacement of
the bone-marrow by a syphilitic connective tissue,
and there was widespread extramedullary haemo-
poiesis. Josephs stressed the rarity with which
syphilitic anaemia was seen at the Harriet Lane
Hospital for children, and mentioned the paucity of
reports of severe anaemia in congenital syphilis from
the U.S.A.

Unlike Josephs’ cases, our infants showed no
replacement of the bone-marrow by syphilitic
connective tissue. Haemolysis if present was
minimal, the most severely anaemic cases having
normal serum bilirubin levels.

The suppression of either megakaryocytes or
platelets probably represents varying degrees of
severity of the infection, and appears to be unrelated
to the stage at which the marrow aspirates were
studied after the commencement of therapy. The
mechanism by which syphilis and infection in
general causes thrombocytopenia is obscure. We
postulate that the infection may either prevent
the formation of megakaryocytes, or in some
way interfere with marrow metabolism and so
prevent the normal development of the platelet
precursors.

The consequences of thrombocytopenia may be
severe: 3 children died and 2 of these showed
visceral bleeding at necropsy. A fourth child
developed hydrocephalus secondary to intra-cranial
bleeding during the acute stage of his illness.
The remaining 11 patients recovered with full
haematological remission. These severe complica-
tions and the good response to therapy make early
diagnosis essential.

With the widespread reports of the reappearance
of syphilis in many parts of the world, it is reason-
able to expect that a proportion of bleeding and
purpura in the newborn and young infant will be
caused by this disease, especially among those
communities where antenatal care is not adequate.

Summary

Thrombocytopenia complicating congenital syphi-
ilis is described in 15 cases. Syphilis is a most
important cause of thrombocytopenia and bleeding
during the first few months of life among African
babies at Baragwanath Hospital. The severe com-
lications which may attend the bleeding diathesis,
and the good response to therapy make early
diagnosis essential.

We are grateful to Dr. S. Wayburne and the Super-
intendent, Baragwanath Hospital, for permission to
publish these case reports. We are indebted to Dr. R.
Cassell of the S.A.I.M.R. for the haematological
studies, and we gratefully acknowledge the helpful criticism of
Dr. L. Taitz, Dr. S. E. Levin, and Dr. H. Stein.

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