Inherited thrombocytopenia with thrombasthenia

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SYNOPSIS A family with congenital thrombocytopenia is described through four generations, where the mode of inheritance appears to be an autosomal dominant.

Spontaneous bruising of varying severity, menorrhagia, and profuse bleeding at operation necessitating transfusion were predominant in the history. Platelet function tests were performed on the various patients. Platelet aggregation by adenosine diphosphate (ADP) was found to be defective, though liberation of platelet factor III and platelet thromboplastic function were found to be normal when corrected for deficient numbers.

Familial thrombocytopenia is a rare condition and only some 10 to 15 case reports appear in the literature; of these, investigation of platelet function has been made in only four families (Quick and Hussey, 1963; Larrain and Etchevery, 1962; Cullum, Cooney, and Schrier, 1967; Bithell, Didisheim, Cartwright, and Wintrobe, 1965).

The following report is of a family with cyclical thrombocytopenia occurring in four generations which was associated with a new type of functional platelet defect.

METHODS

A clinical history was taken and an examination made of all members of the family investigated.

Venous blood was collected with sequestrene anticoagulant except when otherwise stated. Bleeding time was estimated by Duke's method (1912) and Hess's test by Bell's modification. Platelet counts were made by the indirect method of Cramer and Bannerman (1929) and platelet morphology was observed in Romanowsky-stained smears. Clot retraction was estimated by a modification of Macfarlane's method (1939). Platelet thromboplastic activity was assessed by the following methods:—(1) Prothrombin consumption test (Merskey, 1950); (2) thromboplastin generation tests (Biggs and Douglas, 1953); (3) platelet factor III availability test (Hardisty and Hutton, 1965). In these procedures the results were compared with those obtained from suspensions of normal platelets in which the concentrations of cells were adjusted to similar values.

Platelet aggregation by ADP was estimated by mixing 0.2 ml of citrated platelet-rich plasma with 0.1 ml of $10 \mu\text{M}$ adenosine diphosphate. Clumping of platelets was assessed macroscopically after 10 to 15 sec. and with the microscope after one min. (Gaarder, Jonsen, Laland, Hellem, and Owren, 1961)

Partial thromboplastin times were estimated using the kaolin-platelet substitute mixture supplied by Diagen with citrated plasma.

One stage prothrombin time (Quick, 1942) was estimated on citrated plasma using a commercial acetone-dried brain extract (Difco) as a source of extrinsic thrombostatin.

RESULTS

CLINICAL REPORT The tree of the family studied is shown in Figure 1. Two generations are alive and were available for study and seven members have been investigated. Clinical details about those already dead or those who could not be contacted have been assessed from histories obtained from more than one relative.

The results of some of the investigations on the seven members of the family are summarized in Table I. Clinical evidence of excessive bleeding was obvious in all affected members although it was not severe and tended to be cyclical. Episodes of spontaneous bruising were noted to be preceded by a history of sudden tiredness. Menorrhagia was prolonged and excessive in affected females and was the symptom leading to initial hospital investigation; in two patients (H.T. and L.S.), however, the symptoms were not severe enough to lead to investigation until they were 30 years old. Examination did not reveal splenomegaly in any of the patients seen and the only relevant physical finding was intermittent and occasional purpura most obvious on the skin of the legs. Hess's test (1917) was positive and the bleeding time variable, but both were usually abnormal in affected individuals, particularly if there were clinical symptoms. In most affected members of the family, tooth extraction had occasioned prolonged bleeding.
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and in two (H.T. and R.G.) surgery had been a hazard requiring fresh blood transfusion with preserved platelets. The remaining blood counts were normal although affected individuals showed occasional hypochromic anaemia. No evidence of white cell abnormalities was seen although particularly looked for. Bone marrow examination was carried out in two affected members of the family and in both megakaryocytes appeared to be scanty but normal in morphology; the rest of the marrow was normal.

SPECIAL INVESTIGATIONS Platelet thromboplastic activity was investigated specially.

Prothrombin consumption tests These gave results within the normal range in all affected individuals.

Thromboplastin generation tests These gave results in the normal range when corrected for the low platelet numbers.

Platelet factor III Activity was normal in all affected individuals. The platelet factor III index was calculated and values above 25% were found in normal controls and in the affected patients (Table I).

Platelet aggregation Adenosine-diphosphate-induced platelet aggregation was persistently abnormal in all affected members of the family.

Clot retraction was also deficient in affected members and was probably a result of the actual platelet deficiency.

Other tests of clotting function, which included partial thromboplastin times and one-stage prothrombin times, were within normal limits.

DISCUSSION

The family described here included individuals showing a haemorrhagic state in four generations and the haemorrhagic tendency was cyclical but appeared to be persistently related to low platelet counts; the defect appeared to be transmitted as a simple autosomal dominant. Investigations of platelet function in affected members of the family showed that there was no deficiency in their thromboplastin generating activity but an abnormality of

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Patient</th>
<th>Sex</th>
<th>Clinical</th>
<th>Platelet Count (mm³)</th>
<th>Prothrombin Consumption Index (%)</th>
<th>Platelet Factor III Index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H.T.</td>
<td>♂</td>
<td>Affected</td>
<td>40,000</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>W.D.</td>
<td>♂</td>
<td>Unaffected</td>
<td></td>
<td>38¹</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>L.S.</td>
<td>♂</td>
<td>Affected</td>
<td>46,000</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>G.G.</td>
<td>♂</td>
<td>Unaffected</td>
<td></td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>R.G.</td>
<td>♂</td>
<td>Affected</td>
<td>39,000</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>A.T.</td>
<td>♂</td>
<td>Unaffected</td>
<td>72,000</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>B.S.</td>
<td>♂</td>
<td>Unaffected</td>
<td></td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>A.G.</td>
<td>♂</td>
<td>Unaffected</td>
<td>250,000</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>A.G.</td>
<td>♂</td>
<td>Unaffected</td>
<td>620,000</td>
<td>0-30</td>
<td>Above 25</td>
</tr>
</tbody>
</table>

¹The very low platelet count may account for this abnormal figure.
TABLE II
BLEEDING DISORDER CLASSIFIED ACCORDING TO PLATELET DEFECT

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Other Associated Abnormalities</th>
<th>Platelet Number</th>
<th>Platelet Function</th>
<th>Platelet Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Aldrich's syndrome</td>
<td>Sex-linked recessive</td>
<td>Hypogammaglobulinaemia, recurrent infections, eosinophilia</td>
<td>Reduced</td>
<td>Not investigated</td>
</tr>
<tr>
<td>2 Thrombocto- pathy</td>
<td>Dominant</td>
<td>Recurrent infection</td>
<td>Reduced or may be normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>3 Throm- asthenia</td>
<td>Dominant</td>
<td>Nil</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
</tbody>
</table>

their adhesive qualities. These aspects of platelet function have been described as thrombopathic and thrombasthenic respectively (Braunsteiner and Pakesch, 1955) and it is into the last category that members of this family fit. Two main types of inherited thrombocytopenia have been described. One is inherited as a sex-linked defect and is associated with allergy, a tendency to infection, hypogammaglobulinaemia, and often other blood dyscrasias. It is referred to as Aldrich's syndrome (Aldrich, Steinberg, and Campbell, 1954). The other is inherited as a simple dominant and shows only the presence of a haemorrhagic state. This last condition has been reported on a number of occasions (Witts, 1932; Woolley, 1956; Quittner, 1956; Quick and Hussey, 1963; Larrain and Etcheverry, 1962; Cullum et al., 1967).

However, reports of investigations on platelet function in this disorder have recently suggested that there may be a qualitative platelet defect as well. An abnormal prothrombin consumption test has been described in six of the families reported above and an abnormal thromboplastin generation test using the patient's platelets in four (Quittner, 1956, Quick and Hussey, 1963; Larrain and Etcheverry, 1962; Cullum et al., 1967). These tests all indicated an abnormality in platelet thromboplastic activity in association with the thrombocytopenia and were usually associated with abnormal platelet morphology. These findings differ from those found in the family investigated here in which a different type of inherited platelet defect has been found: a failure of platelets to clump under suitable stimulation, such as the presence of ADP, and it would appear reasonable therefore to subdivide the dominant disorder into two types according to the type of platelet defect (Table II). Normal clumping is thought to be a factor in arresting bleeding by platelet plugging and it seems probable that in this family the haemorrhagic tendency was related both to the lack of platelets and their deficient clumping activity. It is possible that the relative mildness of the symptoms in these patients was a result of the normal platelet thromboplastic activity which partly compensated for the thrombocytopenia and thrombasthenia. In this respect Van Creveld and Paulssen (1953) have drawn attention to the importance of platelet thromboplastic activity in the haemorrhagic manifestations of thrombocytopenia, and Hardisty, Dormandy, and Hutton (1964) have described three individual cases of thrombasthenia with normal platelet counts but with a bleeding tendency clinically.

The ultimate cause of the thrombocytopenia in these patients remains obscure. Although no survival studies of platelets were made, it would appear from the appearances of the bone marrow that there was a deficiency of megakaryocytes and that the lack of platelets was therefore more likely to have been a result of a failure in their production than an increase in their destruction.

REFERENCES