FAMILIAL HAEMOPHILIA AND FACTOR VII DEFICIENCY

BY

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(RECEIVED FOR PUBLICATION MAY 12, 1958)

This investigation is reported because of the combination of familial haemophilia and factor VII deficiency and the unusual occurrence of a female haemophiliac.

Cases of combined deficiencies of different clotting factors are extremely rare and up till now there have been reported combinations of haemophilia and factor V deficiency (Koller, 1954), haemophilia and Christmas disease (Soulier and Larrieu, 1953), Christmas disease and factor VII deficiency (Bell and Alton, 1955; Stein and Abrahams, 1956; de Vries, Kettenborg, and van der Pol, 1955), but not of haemophilia and factor VII deficiency.

Female haemophiliacs in the homozygous state have been reported by Merskey (1951), Israels, Lemper, and Gilbertson (1951), and in the heterozygous state by Taylor and Biggs (1957) and Fantl and Margolis (1955), their fathers being completely normal.

The patient reported here is apparently in the heterozygous state since her father had no bleeding phenomena during his life.

Family History

Colin Br. (aged 11) bruised easily when an infant. He was admitted to hospital for the first time in 1949, when 3 years old, with a haematoma of the right calf. On admission in 1951 a diagnosis of haemophilia was made in view of the prolonged plasma clotting time and reduced prothrombin consumption. He was readmitted several times afterwards with haemarthroses of knees and hip.

He was first seen at this hospital in March, 1957, when he was admitted with bruises on his legs and severe prolonged bleeding from the gums. Routine investigations showed only an unexpectedly prolonged prothrombin time (20/14 sec.). He was transfused with 2 pints of fresh A rhesus-negative blood and given vitamin K₁. Next morning the prothrombin time was 15/13 sec. and bleeding was diminished. Several teeth were then extracted and treated in the following days and he was discharged well. Three months later he was readmitted with a few bruises on the legs and bleeding gums. Bleeding subsided with local treatment and vitamin K₁.

Brenda, his sister (aged 10), appears normal without any haemorrhagic manifestations up till now.

Eileen Br., his mother (aged 46), revealed that she had had excessive bleeding during both her deliveries, during and after a hysterectomy, being transfused in order to control haemorrhage, and after tooth extractions at different times.

Frank G. (aged 43), his maternal uncle, has bled since a small child after trauma and tooth extractions, oozing from sockets usually persisting for about three days. In 1948 he had a blow in the abdomen which was followed by severe haematemesis and melaena and he was transfused in order to control the haemorrhage.

Frank G.'s daughter was not available, but according to her father she has no bleeding phenomena.

Cathleen M. (aged 49), his maternal aunt, and her three children, two males and one female, of whom only one male (David) was examined, have no bleeding phenomena.

His grandmother and grandfather had no bleeding phenomena, were not relatives, and in his grandfather's family there were no bleeders. His grandmother's brother was a bleeder and bled to death after trauma. His grandmother's sister was said to be an actual bleeder, but the available evidence was conflicting. Her son died when a child from excessive bleeding.

The pedigree tree (Fig. 1), showing the inheritance of haemophilia and factor VII deficiencies, is based on investigations of the available members of the family. None of those without bleeding history was available for examination.

Laboratory Investigations.—The clinical history of the family is consistent with haemophilia, but the prolonged prothrombin time and the female bleeders made the diagnosis doubtful. The confirmation of the haemophilia and the investigation of the prolonged prothrombin time were therefore necessary. From Table I the bleeding time is obviously normal, while the clotting time (Lee-White mean of four tubes) is slightly prolonged in Eileen Br. and Frank G. Since 1949 repeated estimations of Colin Br.'s clotting times ranged between 4 and 14 minutes, the platelet...
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No bleeding history
Haemophiliacs
Bled to death
Factor-VII-deficient patients

FIG. 1.—Pedigree tree.

 lets between 250,000 and 350,000 and the fibrinogen between 0.18 and 0.31%. The prothrombin time is slightly but definitely prolonged, and Colin Br.’s ranged from 17 to 20 sec. (control 13–14 sec.) on different occasions. The prothrombin time is not corrected with the addition of fresh normal alumina-adsorbed plasma in 10% quantities to the patient’s plasma. Alumina plasma contains adequate amounts of factor V but no prothrombin or factor VII which have been adsorbed by the alumina. A factor V deficiency should therefore be excluded. The prothrombin time is corrected by adding normal stored serum in 10% quantities to

TABLE I
RESULTS OF COAGULATION STUDIES OF THE FAMILY

<table>
<thead>
<tr>
<th></th>
<th>Clotting Time (min.)</th>
<th>Bleeding Time (min. sec.)</th>
<th>Prothrombin Time (sec.)</th>
<th>Prothrombin Time when 10% Normal Adsorbed Plasma Added (sec.)</th>
<th>Prothrombin Time when 10% Normal Serum Added (sec.)</th>
<th>Factor VII (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eileen Br.</td>
<td>15</td>
<td>1 30</td>
<td>16·5</td>
<td>15·5</td>
<td>12·5</td>
<td>60</td>
</tr>
<tr>
<td>Colin Br.</td>
<td>13·5</td>
<td>1 45</td>
<td>18*</td>
<td>18</td>
<td>14</td>
<td>40</td>
</tr>
<tr>
<td>Brenda Br.</td>
<td>9·5</td>
<td>3 30</td>
<td>19</td>
<td>18·5</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>Cathleen M.</td>
<td>11·5</td>
<td>2 15</td>
<td>16·5</td>
<td>16</td>
<td>12·5</td>
<td>--</td>
</tr>
<tr>
<td>David M.</td>
<td>10·5</td>
<td>1 15</td>
<td>18</td>
<td>17</td>
<td>13</td>
<td>45</td>
</tr>
<tr>
<td>Frank G.</td>
<td>17</td>
<td>1 15</td>
<td>17</td>
<td>17</td>
<td>13</td>
<td>50</td>
</tr>
<tr>
<td>Normal</td>
<td>6–13</td>
<td>1–4</td>
<td>13</td>
<td></td>
<td></td>
<td>80–120</td>
</tr>
</tbody>
</table>

* His prothrombin time was 20 sec. during an episode of bleeding.
the patient's plasma. Normal serum contains factor VII but no factor V and only minimal amounts of prothrombin, both being consumed during clotting. Normal serum contains Christmas factor as well, but lack of this factor does not influence prothrombin time. The amount of prothrombin was normal as estimated with the two-stage technique (Biggs and Macfarlane, 1957) in two patients.

It is probable, therefore, that the prolonged prothrombin time is due to factor VII deficiency. This is established because (a) the low level of factor VII as determined quantitatively by Owren's method, (b) the failure to correct the prothrombin time of the patients' plasma when they were crossed with factor VII-deficient serum, and (c) the only partial correction of "dindevan" plasma lacking in factor VII when crossed with the patients' sera (Table II).

Thromboplastin generation (Biggs and Macfarlane, 1957) was abnormal in three members of the family (Table III). In these three patients, by replacing their plasma with adsorbed normal plasma containing antihaemophilic globulin and factor V, or by adding minimal amounts of pure A.H.G. to their plasma, the generation of thromboplastin became normal (Tables IV and V). Mixtures of patients' plasma and known haemophilic plasma did not correct the deficient thromboplastin generation. No anticoagulant has been detected after the incubation of the plasma with normal plasmas or A.H.G. at 37°C.

These results of the thromboplastin generation exclude again factor V and Christmas factor deficiency which might have been responsible for the abnormal generation and establish the antihaemophilic globulin deficiency. They show in addition that factor VII does not influence at all the thromboplastin generation because the latter is normal when using normal plasma and patient's serum deficient in factor VII.

Treatment.—During the acute bleeding fresh blood was given and the haemorrhage controlled. Pure animal anti-haemophilic globulin should be reserved for severe bleeders and serious operations, having in mind the sensitivity that develops and the difficulty of its preparation (Macfarlane, Mallam, Witts, Bidwell, Biggs, Fraenkel, Honey, and Taylor, 1957). Vitamin K₁ was given as well, and in one other instance, when the bleeding was mild, only vitamin K₁. Although it is said to be without any benefit in congenital cases, Newcomb, Matter, Conroy, DeMarsh, and Finch (1956), van Creveld, Veder, and Blans (1956), and Stefanovic, Milosavljevic, and Stefanovic (1955) observed some beneficial response.
Discussion

Haemophilia is a hereditary disease characterized by lack of anti-haemophilic globulin in the blood. The disease appears only in the male since it is transmitted as a sex-linked recessive gene contained in the X chromosomes, and remains occult in the female.

The theoretical aspect that mating of a female carrier and a male bleeder would produce a homozygous active female bleeder has been shown by Brinkhous and Graham (1950) in dog experiments, in the case of Israels et al., and in Merskey's paper in which he reviews the related literature and presents a haemophilic family with intermarriages for generations and actual bleeding in females.

Theoretically again it is impossible for a heterozygous female (carrier) to manifest active haemophilia, but that this also may happen is illustrated in the case of Fantl and Margolis, who reported a female bleeder without paternal family history, in the case of Taylor and Biggs, who could not detect any deficiency of the A.H.G. in the parents of their haemophilic female, and in the present case, where the father of the haemophilic female and his family were normal and were not related to his wife's family. It is characteristic that all these females have a mild haemophilia and the same mechanism may be responsible for its appearance.

Fantl and Margolis try to explain this phenomenon by accepting that the female is heterozygous in respect of the gene responsible for her son's severe condition, but in her own case the trait is incompletely recessive. Taylor and Biggs, however, think that the female is a carrier of severe haemophilia and the remaining gene has been modified to produce mild haemophilia, her son having inherited the latter.

This explanation fits well with the present case, although we can accept as well the possibility of the manifestation of the recessive gene by the simultaneously defective gene for factor VII.

Since Alexander, Goldstein, Landwehr, and Cook's (1951) first description of congenital factor VII deficiencies, 33 more cases have been reported up to date, which can be divided into two groups: (a) familial (17 cases in six families) and (b) congenital, although definite family data for some of these are lacking. These cases are of a definite familial character. All familial cases have normal thromboplastin generation and/or prothrombin consumption with the exception possibly of Wurzel, Roth, and Zubrow's (1954) cases which had slightly abnormal prothrombin consumption. This means that the inherited deficiencies are probably of pure factor VII. The congenital group, with the exception of Hicks (1955), Jürgens (1956), and Jenkins (1954) cases, have an abnormal thromboplastin generation and/or prothrombin consumption, and therefore are considered to have other deficiencies additional to factor VII not yet fully established as separate factors playing a role in blood coagulation.

Telfer, Denson, and Wright's (1956) case is deficient in a factor responsible both for abnormal thromboplastin generation and prolonged prothrombin time (Prower defect).

According to Bachmann et al. (1957), Prower defect and Hougie's (1956) Stuart factor are identical; they reported a similar case with abnormal thromboplastin generation and nearly lacking factor VII, calling the deficiency Prower–Stuart.

It is probably Prower–Stuart factor, and not factor VII, which is responsible for the haemorrhagic phenomena in de Vries et al.'s (1955) and Stefanovic et al.'s (1955) cases with the only mildly impaired prothrombin times and the pathological thromboplastin generation. The patients discussed here, having the same prolongation of prothrombin time, do not bleed probably because the deficiency is of factor VII alone and its level must be very low for the manifestation of bleeding. This does not exclude the appearance of haemorrhagic phenomena in their immediate descendants, having in mind Frick and Hagen (1953) and Long, Letendre, and Colpron's (1955) cases in which the parents of the bleeders were mildly affected but symptomless throughout their lives.

Summary

A family with a condition not previously reported of mild pure factor VII deficiency and haemophilia is presented. A female haemophilic, apparently in the heterozygous state, is included in this family. The literature on the subject is reviewed.

I wish to thank Dr. A. G. Signy for his continuous help and advice, Dr. R. Biggs for providing me with the pure A.H.G., Mr. K. Prentis for his invaluable technical assistance throughout the investigation, and Dr. H. Burkinshaw, under whose care the patient was admitted, for permission to publish this case.

References

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