UNUSUAL TRANSMISSION OF THE
HAEMOPHILIC GENE

BY

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The clinical picture of haemophilia can be simulated by a deficiency of any of the essential factors required for the normal generation of plasma thromboplastin (Biggs, Douglas, and Macfarlane, 1953). The blood-clotting anomaly known as Christmas disease (Aggeler *et al.*, 1952; Biggs *et al.*, 1952) is perhaps the most notable in this respect, for it comprises Bridge anticoagulant (Nour-Eldin and Wilkinson, 1957, 1958) and it is also inherited in a similar manner to classical haemophilia. The method of inheritance of haemophilia as a sex-linked recessive character has been deduced from clinical observations, and was further confirmed when Israëls *et al.* (1951) and Merskey (1951) found haemophilic females whose family histories were in agreement with it. Furthermore, the transmission of haemophilia in dogs (Brinkhous and Graham, 1950) was also found to conform to this pattern.

In the present paper we describe a haemophilic family in whom the disease had been inherited in the usually accepted way, but has deviated from it in the most recent generation.

Methods

Reagents.—Al(OH)₃ suspension was prepared by the method of Quick (1951). Serum, platelet suspension, and plasma were prepared as described by Biggs and Macfarlane (1953). Antihaemophilic globulin was separated from bovine plasma by the citrate and phosphate precipitation method of Bidwell (1955); a solution was used containing 1 mg./ml. 0.9% NaCl.

Blood-clotting tests were carried out essentially as described by Biggs and Macfarlane (1953). For convenience of expression in recording the thromboplastin generation test, the activity at the sixth minute was expressed as a percentage of average normal from a previously constructed dilution curve. Tests of capillary function: the nail-bed capillaries were inspected, magnified 20 times, by a Zeiss binocular dissecting microscope; the Hess test and bleeding-time estimations were carried out as described by Whitby and Britton (1950). Clot retraction was carried out according to Macfarlane (1939). The concentration of fibrinogen was determined as described by Varley (1954). Paper electrophoresis: a barbitone buffer pH 8.6 was used in a vertical tank (Flynn and de Mayo, 1951).

Clinical Features

The family tree is here shown. The individuals numbered in generations IV–VI have been repeatedly examined by us and their personal histories are summarized below (with the exception of IV 2). Unless otherwise stated, clinical examination did not disclose any signs of other disease. Informa-

tion about the previous generations (I–III) was provided by patient IV (E. T.) from careful family records. It will be noted that female haemophiliacs occur in the fifth generation as a result of a first-cousin marriage. The two affected females in the sixth generation are, however, the offspring of the female bleeders (V 2 and V 4) of the fifth generation and normal males showing no clinical or laboratory evidence of haemophilia.

E. T. (IV 1).—Aged 60. This female patient has rheumatoid arthritis. As a young woman she tended to bruise more readily than usual. Her medical history, apart from

Family tree. ■ = Affected males. ● = Affected females. ○ = carriers.

menorrhagia, was not suggestive of any haemorrhagic diathesis. For the last few years she has not had any abnormal bleedings.

A. W. T. (V 1).—Male aged 34. His tonsils were removed during childhood without excessive bleeding. No haemorrhagic tendency has been noticed. He has two healthy children aged 9 and 13 years respectively.

D. C. (V 2).—Female aged 30. This patient gave a history of severe menorrhagia, while repeated attacks of epistaxis have troubled her for a long period. She bruises easily and spontaneously, and protracted haemorrhages have occurred after each tooth extraction. Although her only labour was not complicated by severe haemorrhage, it was succeeded by daily vaginal bleedings for three months.

L. J. T. (V 3).—A male aged 28 with no history of any bleedings even after teeth extractions.

E. R. (V 4).—Female aged 27. She has always bled excessively after dental extractions, the average period in each case being seven days; in one instance, at the age of 12 years, she was admitted to hospital following the extraction of three teeth. Tonsillectomy at the age of 3 years led to a severe and protracted bleeding, in the course of which her life was in danger. She had a severe post-partum haemorrhage following the delivery of her only daughter. Her menstrual loss, although not so severe as that of her sister (D. C.), tends to be excessive. She has always bruised easily and apparently spontaneously, but gave no history of haemarthrosis or of any visceral bleeding.

A. J. T. (V 5).—Male aged 21; has had no trouble with bleeding. As a child he sustained a severe laceration of his leg in a road accident without undue haemorrhage.

F. T. (V 6).—Female aged 15; has had repeated slight epistaxis, but has shown no other haemorrhagic tendencies; teeth have been extracted without incident and her menstrual loss has been normal.

L. C. (VI 1).—Female aged 4; has bruised easily and spontaneously, and on two occasions she has bled excessively from minor lacerations of her buccal mucosa.

J. R. (VI 2).—Female aged 2; is subject to easy and apparently spontaneous bruising. This feature was first noted at the age of 6 months, but she has as yet shown no other manifestations of a haemorrhagic state.

Laboratory Results

	Normal Values	E.T. (IV 1)	A.W.T. (V 1)	D.C. (V 2)	L.J.T. (V 3)	E.R. (V 4)	A.J.T. (V 5)	F.T. (V 6)	L.C. (VI 1)	J.R. (VI 2)	P.C.
Age (years)		60	34	30	28	25	21	15	4	2	34
Blood group (ABO and Rh(D))		O+	B+	B+	A+	B+	A+	A+	O+	A+	
Blood-clotting time (min.)	4-7	5	6	6	5	5	7	7	5½	5½	5½
Prothrombin consumption index (%)	Up to 40, mostly below 10	11	—	44	8	55	—	8	8	—	10
Thromboplastin from Al(OH) ₃ -plasma (%)	90-100	100	100	12	100	5	100	100	15	30	95
Fibrinogen (mg./100 ml.)	200-500	—	—	287	—	376	—	—	—	—	—
Platelets (10 ⁹ /c.mm.)	200-500	291	362	424	401	410	282	314	286	290	—
Bleeding-time (min.)	1½-5	3	5	2½	1½	3	—	5	1½	2	—

P. C.—The husband of D. C. (V 2) and father of L. C. (VI 1). He is in good health, and gave no history of a haemorrhagic state either in himself or in his family other than his daughter. Examinations of his blood did not disclose any blood-clotting anomaly.

Unfortunately the father of J. R. (VI 2) was unavailable for examination, but he is and has been in good health without any history of bleeding episodes, nor was there evidence of any haemorrhagic diathesis in his relatives other than his daughter.

No other members of the family were available for personal study. The histories obtained were consistent with the diagnosis of haemophilia in the male bleeders. Thus A. T. (IV 2), who was the husband and first cousin of E. T. (IV 1), suffered from recurrent haemarthrosis, epistaxis, and melaena necessitating repeated hospital admissions. He eventually died of a massive haemorrhage some years prior to this investigation.

Laboratory Investigations

Blood-clotting tests have been carried out on 10 members of the family listed above. The results of these, together with other relevant data, are presented in the accompanying Table. Quick's one-stage prothrombin time was normal in all samples of plasma. The thromboplastin generation test indicates a deficiency of a plasma factor in four of these individuals. The plasma defect in our patients could be corrected by the addition of normal plasma or plasma from a person with Christmas disease, but haemophilic plasma had no corrective effect. No improvement in the formation of plasma thromboplastin was observed when our patients' plasma was added to that of a known haemophilic patient. In addition, bovine antihaemophilic globulin was found to be effective in correcting the generation of thromboplastin from the plasma of these patients.

The sera of these patients, as tested by the thromboplastin generation test, were normal; Christmas disease was excluded. No circulating anticoagulant could be detected.

All the patients examined gave a negative Hess test, normal blood-clot retraction, and normal findings on capillary microscopy. Serum electrophoresis showed normal bands in all 10 sera examined.

Discussion

The clinical history and mode of transmission of the haemorrhagic diathesis in this family (see Diagram) suggested a diagnosis of either haemophilia or Christmas disease. The clotting defect in the blood obtained from some members of the family was found to be due to a deficiency of antihaemophilic globulin. This has been proved by the thromboplastin generation test (Biggs and Douglas, 1953) as well as by the ability of normal and Christmas disease plasma and isolated antihaemophilic globulin to correct the defect.

As shown in the family tree E. T. (IV 1) has from her first marriage one daughter who is apparently normal. However, on marrying a haemophilic person (her first cousin) two of her daughters were affected, demonstrating that she herself is a carrier; none of her sons have inherited the disease. Nevertheless, the history up to this generation is still in conformity with the theoretical and observed mode of transmission of the haemophilic gene.

The two haemophilic daughters, D. C. (V 2) and E. R. (V 4), who are married to normal persons, have two daughters (VI 1 and VI 2) who are suffering from antihaemophilic globulin deficiency. This was not anticipated, being against the rule of a sex-linked recessive character. Although it is difficult to decide the true nature of this unexpected deviation, certain explanations may be offered.

Sporadic cases of haemophilia, in which inheritance could not be established, seem to occur from time to time (Boggs, 1934). In our series of 185 cases of haemophilia a positive family history could be elicited in 67% only. This might indicate a spontaneous mutation of the sex cells of the female. It thus follows that the occurrence of haemophilia in the two female children in the recent generation of the family described in this paper might be due to a similar mutation of the other X chromosome, resulting in a homozygous female. This possibility seems to be supported also by the presence of both Christmas factor and antihaemophilic globulin deficiencies in one member of a family which previously showed the latter deficiency only (Verstraete and Vandenbroucke, 1955).

Another explanation is that the haemophilic trait in these cases has assumed a dominant character instead of being a recessive one. This inheritance pattern has been reported in some cases showing a vascular abnormality (Singer and Ramot, 1956). Although the latter defect is absent in our cases, and the preceding family history points to the defect as having a recessive character, the presence of the anomaly in two female cousins seems to favour this view.

By analogy with the observations of Hill and Hill (1955) on drosophila, it may also be suggested that the mothers' sex chromosomes might not have separated during meiosis and the resulting zygote in the daughters would be XXX, thus having two affected chromosomes.

Summary

A family is reported with clinical and laboratory findings showing antihaemophilic globulin deficiency.

The presence of the anomaly in two females cannot be explained by the accepted rule of a sex-linked recessive character related to haemophilia.

Possible implications of this abnormal genetic feature are discussed.

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