Combined Hemophilia and Christmas Disease

By J. H. Robertson and Rosemary G. Trueman

In 1952 the investigations of Aggeler et al. and those of Biggs et al. first clearly distinguished hemophilia (AHG deficiency, hemophilia A) from Christmas disease (PTC deficiency, hemophilia B). Since then there have been few reports of the occurrence of the two disorders in the same individual but as both hemophilia and Christmas disease are transmitted as recessive sex-linked characters family studies in such cases are of importance in the understanding of the genetic relationship between the two conditions. They should also be of help in the preparation of a "gene map" of the X-chromosome.

The present report describes a case of combined hemophilia and Christmas disease and the results of a family study.

Methods

Methods used in the investigation of the patients included measurement of the bleeding time, the whole-blood coagulation time, the tourniquet test and the one-stage prothrombin time (Quick) and were as described by Biggs and Macfarlane and Dacie. The thromboplastin-generation screening test of Hicks and Pitney was used, modified in later cases by the addition of a suspension of kaolin to the incubation mixture to ensure maximal activation.

The thromboplastin-generation test was performed using lipoid platelet substitute. The ability of the patient to correct known hemophilic plasma and Christmas serum was assessed by diluting the patient's adsorbed plasma or serum in nine parts of adsorbed known hemophilic plasma or Christmas serum. The thromboplastin generation of the mixture was then compared with that of a similar mixture in which normal plasma or serum were substituted for that of the patient.

Plasma AHG assays were according to the method of Pitney, modified as described by Pitney and Arnold. The patients' plasmas were assayed in relation to a normal plasma which was considered to contain 100 per cent AHG. A previous survey of normal subjects had indicated the lower limit of normal to be 60 per cent of this standard plasma.

Christmas factor assays on serum were performed essentially as described by Biggs et al. The results were expressed in relation to a control of pooled normal serum taken to represent 100 per cent Christmas factor.

An inhibitor of plasma thromboplastin was tested for using the calcium clotting time method.

Case Reports

Combined Hemophilia and Christmas Disease

The patient (IV-8 in fig. 1) was a male aged two years when his first symptom appeared. At this time he bled for two weeks following suturing of a cut on his upper lip. He was seen two years later, his mother complaining that he bruised very easily, often apparently, spontaneously. There was no history of joint symptoms.

From the Department of Haematology, Royal Perth Hospital, Perth, Western Australia. Submitted Aug. 6, 1963; accepted for publication Jan. 24, 1964.

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The initial laboratory investigations gave normal results. The bleeding time was 2', the tourniquet test negative, clotting time 6' and prothrombin time 14" (Control 13''). Platelets appeared normal on the blood film. The thromboplastin-generation screening test was abnormal; however, the patient’s plasma gave a minimum substrate clotting time of 15', with the control being 9". In the full generation test, (fig. 2 and table 1) it was found that although the patient’s plasma alone generated thromboplastin normally, his serum was abnormal and his plasma and serum together showed a marked defect. His serum showed little or no correction of known Christmas serum and his plasma only poor correction of known hemophilic plasma. The presence of a circulating anti-coagulant was excluded by demonstrating full correction of the serum defect when one part of normal serum was added to nine parts of the patient’s serum. In the calcium clotting test addition of a small volume of normal plasma also substantially reduced the patient’s clotting time.

Assay of AHC gave a value of 34 per cent and of Christmas factor 6 per cent of the standard normals.

Family Study

The family tree is shown in figure 1. There was no history of consanguinity.

On most family members examined, a clotting time, bleeding time, tourniquet test, platelet count and one-stage prothrombin time were performed. In all cases these tests gave normal results. In five members, however, either Christmas disease or hemophilia were demonstrated by the thromboplastin-generation test or specific assay. The bleeding symptoms and the results of the laboratory tests on the five subjects are shown in table 1.

Christmas Disease

Case III-4: A maternal uncle of the patient IV-8 and aged 17. When first seen, a serum defect was found in the thromboplastin-generation test and his A.H.G was assayed at 143 per cent of the standard (Dr. W. B. Pitney). Two years later, further investigation has shown his serum to have little or no corrective effect on Christmas serum and a further A.H.G assay has confirmed the previous result. Christmas factor assay gave a value of 10 per cent of the control.

Case III-5: This patient, aged 10 years, was another maternal uncle of IV-8. The thromboplastin-generation screening test gave an equivocal result (minimum substrate clotting time; patient 9", normal control 7") as did his serum in the full generation test. There was, however, little or no correction of known Christmas serum. His A.H.G was assayed at 202 per cent and Christmas factor as 16 per cent of standard normal.
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Fig. 2.—In A., the curves illustrate the results of the thromboplastin-generation test using: ——; normal reagents also patient's plasma with normal serum. ——/—/—/—/—/—; normal plasma with patient's serum. —— ——; patient's plasma with patient's serum. In B. are shown the results of tests using mixtures of hemophilic plasma and Christmas serum with reagents derived from the patient and a control subject. — — — —; hemophilic plasma with normal serum. — — — —; normal plasma with Christmas serum. — — — —; hemophilic plasma + normal plasma with normal serum also normal plasma with Christmas serum + normal serum. — — —; hemophilic plasma + patient's plasma with normal serum. — — —; normal plasma with Christmas serum + patient's serum.

Case III-11: When aged 14 years this boy was found to have an abnormal thromboplastin-generation screening test. The full generation test showed a serum defect with failure to correct Christmas serum (Dr. W. R. Pitney). Recent further tests have confirmed these results and his plasma has been found to correct hemophilic plasma. AHG assay gave a value of 85 per cent and Christmas factor assay 4 per cent of the controls.

Hemophilia

Case IV-1: A male was aged 19 years when he first presented. The thromboplastin-generation screening test was found to be abnormal and his AHG 28 per cent of the control, the assay being repeated on two separate occasions with similar results (Dr. W. R. Pitney). Four years later in a thromboplastin-generation test, his plasma has shown little defect when tested alone but to have only poor ability to correct hemophilic plasma (table 1). Correction of Christmas serum was complete and the Christmas factor was assayed at 100 per cent of normal.

Case IV-3: This 4 year old boy was a cousin of IV-1. His AHG was assayed at 44 per cent of the control. Further investigations have not been possible.
Table 1.—Symptoms, Thromboplastin-Generation Test and Assay Results in Subjects with Hemophilia or Christmas Disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Bleeding Symptoms</th>
<th>HP CS</th>
<th>HP CS</th>
<th>HP CS</th>
<th>AHG%</th>
<th>CF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV-8</td>
<td>Cuts, bruising</td>
<td>20 13</td>
<td>8 8</td>
<td>11 13</td>
<td>34</td>
<td>6</td>
</tr>
<tr>
<td>III-4</td>
<td>Bruising, teeth,</td>
<td>– 12</td>
<td>7 7</td>
<td>8 15</td>
<td>– 11</td>
<td>143 10</td>
</tr>
<tr>
<td></td>
<td>tonsils</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-6</td>
<td>None</td>
<td>– 12</td>
<td>7 7</td>
<td>9 11</td>
<td>202 16</td>
<td></td>
</tr>
<tr>
<td>III-11</td>
<td>Teeth, tonsils,</td>
<td>20 10</td>
<td>7 7</td>
<td>11 11</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>appendix,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV-1</td>
<td>Bruising, epistaxis,</td>
<td>23 11</td>
<td>7 8</td>
<td>9 14</td>
<td>28 100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>joints</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV-3</td>
<td>Bruising</td>
<td>– – –</td>
<td>– –</td>
<td>– –</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>

The minimum substrate clotting time in seconds is shown in systems testing: HP = hemophilic plasma; CS = Christmas serum; N = normal reagents; NP = normal plasma; PP = patient's plasma; PS = patient's serum and mixtures of these. The results of antihemophilic globulin (A.H.G.) and Christmas factor (C.F.) assays are shown in the last two columns.

Of the remaining members of the family I-1, I-2 and II-2 are deceased. I-1 was said to have been a “bleeder” all his life. His wife (I-2) and son (II-2) were apparently unaffected. The latter was killed in the war.

The results of the investigations possible on other members of the family are summarized in table 2. It can be seen that the brother, mother and father (IV-7, III-5 and III-5A) of the combined case (IV-8) were found to be normal. The status of IV-2 is uncertain. His brother, IV-1, has an AHG deficiency and he himself is said to bleed excessively after tooth extraction and to bruise easily. His AHG has previously been assayed at 56 per cent but it was not possible to investigate him further. It is also of interest that three of the females tested (II-3, III-1 and III-2) were found to have rather low AHG levels and that two of these suffered from epistaxis and had trouble with prolonged bleeding after tooth extraction. The male cases of AHG deficiency were either the sons or grandsons of these subjects.

DISCUSSION

Since the first case described by Soulier and Larrieu, there have been a number of reports of combined hemophilia and Christmas disease in the literature. A variety of methods were used in the investigation of these cases and doubt has been raised about the diagnosis in many. Indeed, Graham considered that none of the cases then reported had been shown conclusively to be examples of double hemizygosity for hemophilia and Christmas disease. In the investigation of such cases he emphasized the importance of quantitative assays, of tests for circulating anti-coagulants and of studies showing the independent segregation of the two defects in different members of the family.

In the present case, the diagnosis of a combined deficiency seems fairly well established, being based both upon failure to correct known hemophilic plasma and Christmas serum and on quantitative assays. It is also supported by the finding of both AHG and Christmas factor deficiency occurring sepa-
<table>
<thead>
<tr>
<th>Patient</th>
<th>Symptoms</th>
<th>T.G.S.T.</th>
<th>H.P.↑</th>
<th>A.H.G. %</th>
<th>C.F. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-3</td>
<td>Nil</td>
<td>N</td>
<td>F.C.1</td>
<td>66</td>
<td>—</td>
</tr>
<tr>
<td>II-4</td>
<td>Nil</td>
<td>N</td>
<td>—</td>
<td>90</td>
<td>—</td>
</tr>
<tr>
<td>II-5</td>
<td>Nil</td>
<td>—</td>
<td>F.C.</td>
<td>107</td>
<td>—</td>
</tr>
<tr>
<td>III-1</td>
<td>Epistaxis</td>
<td>—</td>
<td>—</td>
<td>60</td>
<td>—</td>
</tr>
<tr>
<td>III-2</td>
<td>Epistaxis</td>
<td>—</td>
<td>—</td>
<td>57</td>
<td>—</td>
</tr>
<tr>
<td>III-5</td>
<td>Nil</td>
<td>N</td>
<td>F.C.</td>
<td>86</td>
<td>150</td>
</tr>
<tr>
<td>III-5a</td>
<td>Nil</td>
<td>N</td>
<td>—</td>
<td>69</td>
<td>130</td>
</tr>
<tr>
<td>III-8</td>
<td>Nil</td>
<td>N</td>
<td>F.C.</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>III-9</td>
<td>Nil</td>
<td>N</td>
<td>—</td>
<td>145</td>
<td>—</td>
</tr>
<tr>
<td>III-10</td>
<td>Nil</td>
<td>N</td>
<td>—</td>
<td>162</td>
<td>—</td>
</tr>
<tr>
<td>III-12</td>
<td>Nil</td>
<td>N</td>
<td>F.C.</td>
<td>107</td>
<td>—</td>
</tr>
<tr>
<td>IV-2</td>
<td>Bruising</td>
<td>—</td>
<td>—</td>
<td>56</td>
<td>—</td>
</tr>
<tr>
<td>IV-7</td>
<td>Nil</td>
<td>N</td>
<td>—</td>
<td>139</td>
<td>150</td>
</tr>
<tr>
<td>IV-10</td>
<td>Nil</td>
<td>N</td>
<td>F.C.</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* T.G.S.T. = Thromboplastin-generation screening test.
† H.P. C.S. = Correction of hemophilic plasma and Christmas serum.
‡ F.C. = Full correction.
§— = Test not performed.

rately in other members of the family, most of these subjects being tested twice by independent observers.

In the affected members of the family, the symptoms of bleeding are mild and the reduction of AHG or Christmas factor only moderate. It was also found that some of the female carriers of the AHG deficiency had themselves rather low levels of this factor. Von Willebrand's disease, being carried by an autosomal gene, so affects both sexes and may also be associated with a deficiency of AHG or Christmas factor. However, in none of the affected members of the present family was there a prolonged bleeding time or evidence of increased capillary fragility to suggest this condition. The pattern of transmission is also suggestive of a sex-linked recessive inheritance in keeping with classical hemophilia and Christmas disease.

It is now well recognized that both hemophilia and Christmas disease may occur in mild form. Patients described by Pitney and Aggeler et al. had AHG levels similar to those of the present cases. In the family described by Graham et al. about half of the female carriers of mild hemophilia were found to have markedly reduced levels of AHG. This reduction was thought to be a characteristic of the mild disease contrasting with normal levels in carriers of severe classical hemophilia. In the present family, the mothers of the hemophilic patients were found to have rather low levels of AHG with however, the exception of III-5 the mother of the propositus. Similar variations between the AHG levels of carrier females in the same family...
have been noted by others (Graham et al., Pitney and Arnold). The reason for them is uncertain but they perhaps reflect differences in the ability of the normal paired X-chromosome to modify the expression of the hemophilic gene.

The mildness of symptoms in the combined case (IV-8) is surprising. Deficiency of two factors could be expected to summate and produce a marked defect in thromboplastin formation. However, this boy's symptoms have so far shown little difference in severity from those of other members of the family with a single deficiency.

The relative positions of the genes for hemophilia and Christmas disease on the X-chromosome is uncertain. Wiener believed that they might be allelic. On the basis of an estimation of gene frequencies, Graham considered that if each disease resulted from substitution at a single and discrete locus double hemizygosity for hemophilia and Christmas disease would be unlikely to be observed in the billion or so males of the world's population. He felt that in view of the previous reports of combined deficiency pseudo-allelism was a possibility. However, this calculation is necessarily dependent on a number of assumptions which may not be valid. For example, it is perhaps doubtful whether mating of affected individuals will be random as the common bond of bleeding may draw their families together. More recently, evidence has been found that the two genes are in fact well separated on the X-chromosome.

The available data on the present family is capable of several interpretations as to the manner of inheritance of the two disorders. It seems most likely that III-5, mother of the combined case, carries both abnormal genes on one X-chromosome. His grandmother, II-3, may also be in the coupling phase but the finding of single defects in her two sons and the descendents of her sisters suggests that the genes for the two diseases are present on different X-chromosomes. This would indicate that the coupling of the genes in III-5 was the result of a cross-over involving the X-chromosome and be consistent with the view that their loci are quite separate on the chromosome. In this view it also seems probable that the grandmother, II-3, has received an abnormal X-chromosome from each of her parents, I-1 and I-2. The abnormal gene from I-1, whether it be for hemophilia or for Christmas disease, must also be present in all the females of generation II. This implies that either Christmas disease can be expected to appear in the later descendents of II-1 or hemophilia in those of II-5.

It is felt that investigation of further descendents of this family with a study of other genetic "markers" on the X-chromosome, such as the Xg blood group system, might provide information of value in the preparation of a "gene map" of the chromosome.

**Summary**

A case of combined hemophilia (AHG deficiency) and Christmas disease is described. Five other members of the family had either hemophilia or Christmas disease.
The manner of inheritance of the two disorders was uncertain but it was considered most probable that in the mother of the combined case, coupling of the two genes had resulted from a cross-over involving the X-chromosome. It is believed that the findings are consistent with the view that the hemophilia and Christmas disease genes have quite separate loci on the X-chromosome.

Summary in Interlingua

Es describite un caso de hemophilia (carentia de globulina antihemophilic) e morbo Christmas in combination. Cinque altere membros del mesme familia habeva hemophilia o morbo Christmas.

Le maniera del transmission genetic del duo disordines esseva incerte, sed il pareva le plus probabile que in le matre del patiente, un accopulamento del duo genes habeva resultate de un cruciamento concernente le chromosoma X. Es opinate que le constatationes es compatibile con le notion que le gen de hemophilia e le gen de morbo Christmas ha integremente separate locos in le chromosoma X.

Acknowledgments

We wish to thank Dr. W. R. Pitney for permission to quote the results of his investigations on some of the patients. We are also grateful to Dr. R. L. Kirk for valuable discussions on the genetic aspects of the pedigree.

References


J. H. Robertson, M.D., M.R.C.P.E., M.C. Path., Haematologist, Royal Perth Hospital, Perth, Western Australia; Presently Senior Registrar, The Laboratories, Belfast City Hospital, Belfast, Northern Ireland.

Rosemary G. Trueman, A.I.M.L.T., Technician, Department of Haematology, Royal Perth Hospital, Perth, Western Australia.
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J. H. ROBERTSON and ROSEMARY G. TRUeman