Hageman Trait (Factor XII Deficiency): A Probable Second Genotype Inherited as an Autosomal Dominant Characteristic

By Bruce Bennett, Oscar D. Ratnoff, James B. Holt, and Harold R. Roberts

A family is described in which Hageman trait appeared to be inherited in an autosomal dominant manner in contrast to previously reported families in which the disorder behaves as an autosomal recessive characteristic. Immunologic studies suggested that the molecular defect was similar to that of the autosomal recessive form and consisted of deficiency of antigens related to Hageman factor.

HAGEMAN TRAIT is a hereditary disorder of blood coagulation in which plasma is deficient in Hageman factor (Factor XII) as measured by functional assays for its procoagulant, inflammatory, and fibrinolysis-enhancing properties. Currently available evidence suggests that synthesis of Hageman factor is depressed in individuals with Hageman trait, because their plasma is deficient in antigens detectable by antiserum directed specifically against Hageman factor. In the cases thus far reported, Hageman trait appears to be inherited in an autosomal recessive manner. Thus, both sexes are affected with equal frequency; only about one-fourth of the siblings of probands have the disorder; instances of Hageman trait within a family are limited to siblings; and consanguinity between parents of affected individuals is relatively frequent. Anomalously, Hageman trait was detected in three successive generations in one family, but this apparent exception to autosomal recessive inheritance appeared to be explained by a high frequency of consanguinity. We report here studies in a family in which Hageman trait seems to be inherited as an autosomal dominant characteristic.

FAMILY STUDY

The family presented in both Cleveland and Chapel Hill. The Cleveland proband (III-10) is a 6-yr-old boy who was found to have an abnormally long whole-blood clotting time during routine investigation before a proposed tonsillectomy. He had no history of abnor-
Fig. 1. Pedigree of the family studied. The numbers within the symbols indicate Hageman factor concentrations in units per milliliter in the subjects' plasma.
mal bleeding after circumcision, routine immunization, a minor head injury, and dentition. Coagulation studies demonstrated that the clotting time of whole blood was prolonged in glass tubes (75 min; normal, 17–31 min) but was normal in polystyrene tubes (185 min; normal, 75–235 min). The activated partial thromboplastin time was greater than 470 sec (control, 47 sec). Specific assays utilizing a modified partial thromboplastin technique demonstrated that the concentration of Hageman factor was less than 0.01 units/ml (normal average, 1.0 unit/ml), while that of plasma thromboplastin antecedent (PTA, factor XI) was normal.

The Chapel Hill proband (III-7) is a 13-yr-old boy whose clotting time was found to be prolonged prior to tonsillectomy. He gave no history whatsoever of unusual bleeding. A partial thromboplastin time (unactivated) was greater than 200 sec (control, 55.6), and a specific assay for Hageman factor revealed a level of less than 0.01 unit/ml (normal, 1 unit/ml). Factor VIII level was 2.04 units/ml (normal, 1 unit/ml). The patient underwent tonsillectomy without excessive hemorrhage.

Relatives of the patient were traced and tested in Cleveland and Chapel Hill (Fig. 1). The family originated in northeast Kentucky; members of the second and third generation live in Cleveland and Virginia. The family is unaware of a history of consanguinity. The only individual with a history of troublesome bleeding is the paternal grandmother of the propositus (I-4), who once bled severely after dental extraction, but she does not appear to have Hageman trait. In all, seven individuals were detected in whom plasma contained less than 0.01 units of Hageman factor per ml, while in four others the concentration of Hageman factor was 0.3, 0.25, 0.23, and 0.19 units/ml respectively.

The presence of antigens related to Hageman factor was sought by two methods. The plasmas of subjects II-10 and III-10, whom the concentration of functional Hageman factor was less than 0.01 units/ml, contained no antigens detectable by double diffusion in agarose gel against specific, absorbed rabbit antiserum. Precipitin lines were detected in the plasma of normal individuals and of subjects I-3, I-4, and II-11.

Specific antiserum inhibits the procoagulant activity of Hageman factor, while absorption of the antiserum with normal plasma blocks this inhibitory property. In contrast, the plasma of subjects II-10 and III-10, lacking detectable functional Hageman factor, did not block the inhibitory property of the antiserum. The plasma of subject I-3, whose plasma contained 0.30 units/ml of functional Hageman factor, blocked the antiserum to an intermediate degree. The results of these immunologic studies do not differ from those reported previously in Hageman trait.

Discusson

In the family described, evidence of Hageman factor deficiency was detected in three generations and in both sexes, suggesting that the disorder was inherited as an autosomal dominant characteristic. Four of the 11 affected individuals had levels of Hageman factor between 0.19 and 0.30 units/ml. These values are similar to those found in 12 known heterozygotes of the usual autosomal recessive type of Hageman trait (i.e., parents of subjects with Hageman trait) in whom the range of values was from 0.14–0.79 units/ml, and other authors have reported similar findings. In the plasma of normal individuals the concentration of Hageman factor has been found to vary from 0.36–1.52 units/ml. The possibility, however, that this family has the usual autosomal recessive form of Hageman trait appears statistically remote because this would require that subjects I-4, II-8, II-11, who married into the family, should be heterozygotes also. These individuals were unrelated, came from different areas, and had levels of Hageman factor of 1.00 units/ml. The intermediate levels noted in four of the family members suggests, rather, an incomplete expression of the disorder. The immunologic studies reported indicate that this disorder cannot at present be differentiated at a molecular level from that of individuals with the usual autosomal recessive form of the disorder.

These studies suggest, then, that Hageman trait may be placed in the com-
Table 1. Antibody Blocking Activity of Plasma of Subjects in Family Studies Compared
With That of a Subject With Established Hageman Trait and With Pooled Normal Plasma

<table>
<thead>
<tr>
<th>Rabbit Antiserum to Hageman Factor</th>
<th>Clotting Time in Final Hageman Factor Assays (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Subject 3-10</td>
<td>173</td>
</tr>
<tr>
<td>+ Subject 11-10</td>
<td>154</td>
</tr>
<tr>
<td>+ Subject I-3</td>
<td>120</td>
</tr>
<tr>
<td>+ Established Hageman trait</td>
<td>146</td>
</tr>
<tr>
<td>+ Pooled normal plasma</td>
<td>65</td>
</tr>
<tr>
<td>+ PTA-deficient plasma</td>
<td>63</td>
</tr>
<tr>
<td>+ Buffer</td>
<td>135</td>
</tr>
<tr>
<td>Normal Rabbit Serum</td>
<td></td>
</tr>
<tr>
<td>+ Subject number 3-10</td>
<td>59</td>
</tr>
<tr>
<td>+ Pooled normal plasma</td>
<td>49</td>
</tr>
<tr>
<td>+ Buffer</td>
<td>48</td>
</tr>
</tbody>
</table>

Rabbit serum, diluted appropriately, was incubated with plasma samples detailed above (which had been adsorbed with calcium phosphate and heated at 56°C for 30 min to destroy or remove clotting-factor activity other than Hageman factor) for 30 min at 37°C and overnight at 4°C. The mixtures were centrifuged to remove any precipitated material and further heated for 30 min at 60°C to destroy any residual clotting activity. Equal volumes of diluted PTA-deficient plasma (adsorbed with aluminum hydroxide) as a source of Hageman factor were added to aliquots of the mixtures and incubated at room temperature for 45 min; Hageman factor assays were then performed by a coagulation method using known Hageman-factor-deficient plasma as substrate.

pany of deficiencies of antihemophilic factor (factor VIII) and fibrin-stabilizing factor (factor XIII), both of which may be inherited in more than one way.

REFERENCES

12. —: Unpublished observations.
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