A Clinical and Experimental Study of Acquired Inhibitors to Factor VIII

By Harold R. Roberts, Margaret B. Scales, John T. Madison, William P. Webster and George D. Penick

CIRCULATING anticoagulants directed against Factor VIII (antihemophilic factor, AHF) have been reported to occur spontaneously in otherwise normal individuals. Similar anticoagulants have also been observed following penicillin reactions, during or after pregnancy, and in patients with temporal arteritis, lupus erythematosus and rheumatic heart disease. In most instances, however, inhibitors to Factor VIII develop in patients with severe hemophilia A (classic hemophilia, Factor VIII deficiency). Patients with mild classic hemophilia have also been reported to develop an inhibitor to Factor VIII.

Most of the anticoagulants developing in patients with classic hemophilia have been shown to inhibit Factor VIII specifically in a reaction dependent on both time and temperature. Although many investigators have considered Factor VIII inhibitors to be antibodies, the time and temperature dependence of the Factor VIII-inhibitor reaction has suggested to some that the inhibitor was an enzyme.

Recently we studied four patients with classic hemophilia who developed circulating anticoagulants specific for Factor VIII. One patient with a high plasma titer of inhibitor was studied extensively. Our results indicate that (1) the inhibitor can be detected and characterized by a relatively simple modification of the partial thromboplastin time test, (2) intravenous injection of the inhibitor can produce transient Factor VIII deficiency in experimental animals, and (3) the inhibitor possesses properties suggesting that it is an antibody. In addition, our experience with these patients indicates that bleeding hemophiliacs with a potent Factor VIII inhibitor can be successfully treated by employing exchange transfusions.
MATERIALS

Fresh whole blood was collected from normal donors in plastic bags (Fenwal) containing ACD solution. The blood was type specific for ABO group and Rh. All donor cells were cross-matched with the sera of the recipients; donor sera were screened for atypical antibodies using commercial reagent cells. Blood was transfused within 6 hours after collection. Human hemophilic plasma was collected by plasmapheresis in 4 per cent sodium citrate from patients with severe hemophilia A. Porcine antihemophilic factor was obtained from S. Maw Son and Sons Ltd., Barnet, England.

Inhibitor

The inhibitor source was plasma or serum from each of four patients with severe hemophilia A who had a high titer of circulating anticoagulant activity. Most of the data reported here were obtained from patient B. H., who had the highest titer of a circulating anticoagulant. However, the inhibitor activity in plasmas of all patients was shown to have the same characteristics. Partially purified inhibitor material was prepared by cold ethanol fractionation of plasma and by precipitation of non-gamma globulin plasma components with Rivanol. Inhibitor plasma and human hemophilic plasma used for injection into dogs was concentrated by dialysis against a 16 per cent solution of polyvinylpyrrolidone in normal saline for 12 to 18 hours. In general, 100 ml of plasma was concentrated to 25-30 ml by this procedure.

METHODS

Clotting Studies

The following were performed: modified Lee-White clotting times (C. T.), one-stage prothrombin time (PT) tests, partial thromboplastin time (PTT) tests, two-stage prothrombin assays, fibrinogen determinations, platelet counts, Ivy bleeding times, platelet agglutination tests, thromboplastin generation tests (TGT), and specific assays for Factors V, VII, VIII, IX, and X. Factor XII assays were performed in a manner similar to that described for Factor VIII, except that Factor XII deficient plasma was used as substrate. Inhibitor titers were determined as follows: (1) serial dilutions of inhibitor plasma or serum were made with buffered saline; (2) 0.05 ml of each dilution was added to 0.05 ml of normal plasma and a PTT performed immediately and again after incubation at 37 C. for 60 minutes. The inhibitor titer was considered to be the greatest dilution of inhibitor which prolonged the PTT of normal plasma at least 30 seconds after incubation at 37 C. for 1 hour.

Specific assays for Factors V, VII, VIII, IX, X and XII were performed on normal plasma incubated with inhibitor plasma at 28 C. for 60 minutes. To measure these procoagulants accurately it was necessary that inhibitor concentration not be in excess of that amount required to neutralize the Factor VIII in a given sample of normal plasma. When excess concentrations of inhibitor were added to normal plasma, residual procoagulants could not be accurately measured because Factor VIII activity in the substrate plasmas used for specific assays was neutralized. Inhibitor plasma was diluted with either citrated normal plasma or citrated imidazole-saline buffer, pH 7.2. The concentrations of inhibitor material used in these studies were determined by trial and error. Control assays were performed on normal plasma under conditions similar to those described above except that human hemophilic plasma without inhibitor was substituted for inhibitor plasma.

Immunologic Studies

Precipitin reactions were carried out according to the method outlined by Oudin. Hemagglutination studies were performed as described by Stavitsky.
STUDY OF ACQUIRED INHIBITORS TO FACTOR VIII

Canine Studies

Varying amounts of inhibitor plasma which had been concentrated by dialysis against polyvinylpyrrolidone were injected into healthy male and female mongrel dogs. Appropriate control studies were carried out by substituting concentrated plasma from a patient with classic hemophilia who did not have a circulating inhibitor. Clotting studies were performed before injection and at varying time intervals after injection.

RESULTS

Table 1 is representative of clotting studies on hemophilic patients with circulating anticoagulants. The most striking findings were prolonged clotting and partial thromboplastin times, a Factor VIII concentration of less than 1 per cent of normal, and prolongation of the PTT of normal plasma by the patient's plasma when incubated at 37 C. for 60 minutes. Factor XII (Hageman factor) was consistently found to be approximately 45 per cent of normal. Other procoagulants, except Factor VIII, were in the normal range. The PT and thrombin clotting times were consistently normal and protamine sulfate failed to neutralize the inhibitor. Although not shown in the table, the TGT demonstrated plasma and serum defects. Both plasma and serum possessed anticoagulant activity. Platelet agglutination with thrombin was not impaired.

Demonstration of Inhibitor Using the PTT Test

Normally, the PTT of a mixture of hemophilic and normal plasma should not be more than 8 to 10 seconds longer than the PTT of normal plasma alone. When the PTT on a mixture is 25 to 30 seconds longer than the control, an inhibitor is usually present. Figure 1 shows a series of partial thromboplastin times on patient plasma, normal control plasma, and a mixture of the two, before and after the patient received transfusions of fresh normal plasma. Beginning on the sixth day after initiation of transfusion therapy, the PTT on the mixtures gradually lengthened, indicating the development of significant quantities of a circulating anticoagulant. Figure 1 also shows that infusion of normal plasma initially corrected the PTT of the patient's plasma but failed to do so 7 days after the initial transfusion. This is another indication of the presence of a circulating anticoagulant.

Titration of the Inhibitor

Figure 2 shows the partial thromboplastin times obtained when inhibitor plasma, either undiluted or diluted to various concentrations, was mixed with an equal volume of undiluted normal plasma. From the figure it can be seen that at high concentrations of inhibitor, the PTT of normal plasma was prolonged to hemophilic levels, but as the inhibitor concentration was decreased by dilution, the PTT of the normal plasma approached that of the control. The figure also demonstrates that the anticoagulant effect was more marked after 60 minutes incubation than it was without incubation, indicating that the action of the anticoagulant is time dependent.
Table 1.—Clotting Function Tests on a Patient with an Inhibitor to Factor VIII

<table>
<thead>
<tr>
<th>Tests</th>
<th>Patient</th>
<th>Normal Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting time</td>
<td>42 min</td>
<td>10 min.</td>
</tr>
<tr>
<td>Prothrombin time (PT)</td>
<td>12.1 sec.</td>
<td>12.3 sec.</td>
</tr>
<tr>
<td>Partial thromboplastin time (PTT)</td>
<td>323.0 sec.</td>
<td>76.8 sec.</td>
</tr>
<tr>
<td>PTT on mixture of equal parts of patient and control plasma (incubated 60 min. at 37 C.)</td>
<td>220.0 sec.</td>
<td>82.0 sec.*</td>
</tr>
<tr>
<td>Thrombin clotting time</td>
<td>14.4 sec.</td>
<td>14.1 sec.</td>
</tr>
<tr>
<td>Residual prothrombin at 1 hr.</td>
<td>100.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Platelet count</td>
<td>357,500/cu. mm.</td>
<td>257,000/cu. mm.</td>
</tr>
<tr>
<td>Tourniquet test</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>Bleeding time (Ivy)</td>
<td>3½ min.</td>
<td>4 min.</td>
</tr>
<tr>
<td>Clot retraction</td>
<td>normal (1 and 24 hr.)</td>
<td>normal (1 and 24 hr.)</td>
</tr>
<tr>
<td>Platelet function in thromboplastin generation</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Platelet agglutination</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Assays††</td>
<td>Factor I</td>
<td>438 mg.%</td>
</tr>
<tr>
<td></td>
<td>Factor II</td>
<td>487 units</td>
</tr>
<tr>
<td></td>
<td>Factor V</td>
<td>129%</td>
</tr>
<tr>
<td></td>
<td>Factor VII</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>Factor VIII</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>Factor IX</td>
<td>179%</td>
</tr>
<tr>
<td></td>
<td>Factor X</td>
<td>173%</td>
</tr>
<tr>
<td></td>
<td>Factor XII</td>
<td>45%</td>
</tr>
</tbody>
</table>

*Normal control in this instance was obtained by incubating normal plasma with Factor VIII deficient plasma which did not contain an inhibitor.
†Assays on the patient’s plasma were performed at high dilutions in order to circumvent the action of the anticoagulant on the substrate plasma.
††Per cent values refer to per cent of a standard normal control, arbitrarily designated as 100 per cent.

Specificity of Inhibitor for Factor VIII

The circulating anticoagulant which develops in patients with hemophilia A seems to inhibit Factor VIII specifically. In figure 3 it may be seen that when a suitable concentration of inhibitor material was mixed with normal plasma, its only effect was to neutralize Factor VIII activity while the activity of other procoagulants remained at high levels.

Other evidence indicating that the circulating anticoagulant is specific for Factor VIII is shown in figure 4. As can be seen, the PTT of normal plasma becomes progressively longer when inhibitor material is added and is corrected only by adding a source of Factor VIII—e.g., BaSO₄-adsorbed or whole normal plasma. Hemophilic plasma or normal serum did not correct the prolonged PTT.

The best evidence for specificity of the inhibitor was obtained by injecting it into normal dogs and determining its effect on the recipient animal’s Factor VIII levels. Figure 5 is representative of four experiments in which 25–30 ml. polyvinylpyrrolidone-concentrated plasma, obtained from patient B. H., were
Fig. 1.—Development of an inhibitor in response to plasma transfusion. The top curve depicts initial shortening of the PTT followed by refractoriness to plasma 6 days later. Lengthening of the PTT on plasma mixtures (middle curve) establishes the presence of an inhibitor.

injected into normal dogs. As can be seen, following injection of inhibitor plasma, the dog's Factor VIII concentration was reduced to nearly 0 per cent within 3 hours. On the other hand, circulating levels of Factors IX and XII were unaltered. Although not shown in the figure, all other clotting components, including platelets, remained normal. Thus, there was no evidence that the Factor VIII decrease was secondary to intravascular coagulation. In three control experiments, dogs injected with human hemophilic plasma that did not contain an inhibitor, but which was concentrated in the same manner as the inhibitor plasma, showed no decrease in the plasma concentration of Factor VIII or any other plasma procoagulant.

Properties of Inhibitor

It is evident from figures 2 and 4 that the PTT of normal plasma was progressively prolonged when plasma was incubated with Factor VIII inhibitor. To demonstrate that the inhibitor progressively inactivates Factor VIII, it is necessary that the inhibitor be present in low concentrations. At high concentrations the inhibition of Factor VIII occurs so rapidly that it may not be possible to detect the time dependence of the inhibitor—Factor VIII interaction. The effects of high and low concentrations of inhibitor on the PTT of normal plasma are shown in figure 6. It may be seen that at high inhibitor
Fig. 2.—The effect of various dilutions of Factor VIII inhibitor on the PTT of normal plasma before and after incubation at 37°C.

Fig. 3.—Procoagulant levels of normal plasma after addition of an appropriate dilution of inhibitor plasma. The procoagulant levels of the normal plasma prior to the addition of the inhibitor were 100 per cent of a normal control. The final concentration of inhibitor plasma in this experiment was 0.4 per cent (0.2 ml. of inhibitor plasma diluted 1:50 was added to 0.8 ml. normal plasma).
Fig. 4.—Effect of diluted inhibitor on the PTT of normal plasma. Diluted inhibitor and plasma were mixed in a ratio of 1:1. The effect of 1 part of hemophilic plasma, normal plasma, normal serum, or BaSO₄ adsorbed plasma on 1 part of normal plasma-inhibitor mixture is shown on the graph.

Fig. 5.—The effect of the intravenous injection of Factor VIII inhibitor into a normal dog (12 Kg.). Twenty-five ml. inhibitor plasma, concentrated from 100 ml. of plasma from patient B. H., was injected.

Concentrations the PTT was almost immediately prolonged, whereas at low concentrations the PTT was initially normal but was progressively prolonged over a period of 40 minutes. Other physicochemical studies of the Factor VIII inhibitor revealed it to have maximum inhibitory effect when incubated with a Factor VIII source at 37 C. but little effect when incubated at 0 C. The inhibitor was stable over a pH range from 4 to 11 and at temperatures up to 56 C. for 30 minutes. Inhibitor activity was present in plasma and serum and was not adsorbed by BaSO₄ or Al(OH)₃. After Rivanol precipitation of plasma proteins, most of the inhibitor activity was recovered in the supernate. Gamma globulins, prepared by Cohn fractionation of plasma, contained virtually all of the inhibitor activity.
Immunologic Studies

Repeated precipitin tests were negative. Plasma with an inhibitor titer of 1:512 to 1:2048 was used as antibody. Fresh, normal, citrated plasma or a purified human Factor VIII preparation were used as antigens.

In other studies, tanned human red cells were incubated with fresh normal citrated plasma as a source of antigen. Hemagglutination was repeatedly observed when inhibitor plasmas or sera with titers ranging from 1:512 to 1:2048 were added to the washed red cells coated with plasma proteins. All the high titer inhibitor plasmas and sera were obtained from patient B. H. on four different occasions over an 18-month period. Plasma and serum from B. H., when his inhibitor titer was lower, or from the other patients in this study whose inhibitor titers remained below 1:512, did not cause hemagglutination.

Hemagglutination titers ranged from 1:4 to 1:16 and were not correlated with the anticoagulant titers. Complement was not necessary for the reaction. The usual controls were employed in the hemagglutination technic. Addition of fresh normal plasma to the system inhibited all positive hemagglutination reactions. In addition, plasma or serum from hemophilic patients without inhibitors and from other patients who had received numerous transfusions did not cause agglutination of the sensitized cells.

The red cell sensitizing property of fresh normal plasma possessed properties suggesting its identity with Factor VIII—i.e., it gradually disappeared during incubation at 56 C. and was completely gone after 20 minutes at this temperature. It was not present in aged serum, gamma globulin fractions, albumin, or in plasma from two patients with severe hemophilia A. Purified human

Fig. 6.—Partial thromboplastin times on a 1:1 mixture of normal plasma and inhibitor plasma diluted 1:2 or 1:64. Inhibitor plasma, with a titer of 1:512, was from patient B. H. The partial thromboplastin time on a 1:1 mixture of normal plasma and buffer shortened over a 40 minute incubation period.
and canine Factor VIII fractions could not be used to sensitize tanned cells since both preparations caused lysis of the tanned red cells.

The immunologic nature of the inhibitor response was further suggested by the finding that transfusion of plasma or fractions with Factor VIII activity into a hemophiliac with a low or negligible inhibitor titer elicited a rise in inhibitor concentration within 6 to 7 days. This observation was possible only in patients with a low initial titer, presumably because higher concentrations of inhibitor neutralized the transfused Factor VIII before it could exert an antigenic effect.

Effect of Exchange Transfusion and Administration of Purified Animal Factor VIII on Inhibitor Titer

Patient B. H. was admitted to the hospital with severe retroperitoneal bleeding, hematuria, and a progressively falling hematocrit. His incubated inhibitor titer before replacement therapy of any sort was 1:32. After 5 units of fresh-frozen plasma the inhibitor titer decreased to 1:16. After 2 days and 13 units of fresh plasma the inhibitor titer was still 1:16. On the third hospital day the patient's condition suddenly became worse, hematuria increased, the abdomen became more distended, and the hematocrit dropped precipitously. X-ray studies suggested that the retroperitoneal hematoma had extended into the chest. At this time it was elected to perform an exchange transfusion using citrated fresh blood. The exchange was carried out in the operating room via a double lumen catheter inserted into the inferior vena cava through a femoral cut-down site. The description and use of a double lumen catheter has been previously reported.39 Twenty units of blood were removed and 22 units infused during the course of the exchange. Calcium was replaced by giving 10 ml. of a 10 per cent calcium gluconate solution per 1 liter of fresh blood. Electrocardiographic monitoring revealed no abnormalities during the 4-hour period of the exchange. The patient tolerated the procedure well and at the end of the exchange the inhibitor titer dropped so that it was undetectable without incubation and was measured at 1:2 to 1:4 with incubation (table 2). His clotting time returned to normal (3 minutes). His PTT was reduced to 150 seconds and a PTT on a mixture of patient and normal plasma (without incubation) was normalized.

Following the exchange transfusion, the patient's hematuria cleared abruptly and the hematocrit remained stable. However, because of the patient's critical condition and in order to insure hemostasis before a marked increase in the inhibitor titer occurred, the patient was given purified, concentrated porcine Factor VIII; five ampules were given on the first post-exchange day and 12 ampules on the second. One ampule of the porcine material, containing 200 Oxford units of Factor VIII, has been calculated to be equivalent to 800 ml. of human plasma. The porcine Factor VIII fraction reduced the patient's PTT to normal levels but its effect was transient. In table 2 is shown the response of the patient's inhibitor titer. By the seventh day after the exchange transfusion the incubated inhibitor titer had risen to 1:2048. The increase in inhibitor concentration was not prevented by 120 mg. prednisone a day, even though administration of this drug was begun before he received plasma or Factor VIII fractions. In spite of the increase in anti-coagulant titer the patient continued to do well and was subsequently discharged to an active life at home.

Discussion

Although other investigators have postulated that Factor VIII inhibitors developing in patients with hemophilia A are antibodies to Factor VIII,9,20 their immunologic nature has not been definitively demonstrated. Indeed, the findings that the reaction between inhibitor and Factor VIII is progressive
Table 2.—Exchange Transfusion in a Hemophilia A Patient with Circulating Anticoagulant (11.0 liters whole blood exchanged)

<table>
<thead>
<tr>
<th></th>
<th>C.T.</th>
<th>PTT Unincubated</th>
<th>PTT Incubated</th>
<th>HTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before exchange transfusion</td>
<td>&gt;30 min.</td>
<td>230 sec.</td>
<td>1:2</td>
<td>1:16</td>
</tr>
<tr>
<td>After exchange transfusion:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediately</td>
<td>3–5 min.</td>
<td>150 sec.</td>
<td>&lt;1:2</td>
<td>1:2–1:4</td>
</tr>
<tr>
<td>7 days*</td>
<td>—</td>
<td>&gt;200 sec.</td>
<td>1:128</td>
<td>1:2048</td>
</tr>
</tbody>
</table>

*Porcine Factor VIII fraction administered during interim. See text for details.

and temperature dependent have suggested to some that the inhibitor is an enzyme.19 The positive hemagglutination tests reported here suggest that the inhibitor is an antibody. Plasmas or sera without inhibitor or with low titer inhibitor activity did not cause agglutination of sensitized cells. The red cell sensitizing property possessed the characteristics of Factor VIII with regard to its heat stability and its absence in serum, hemophilia A plasma, gamma globulin fractions and albumin. Hemagglutination titers may have been low because Factor VIII is present in only trace amounts in fresh normal citrated plasma with which the red cells were sensitized. In a similar study40 hemagglutination titers ranging from 1:160 to 1:1280 were found in three patients with specific inhibitors of Factor IX. The antigens used were purified fractions with a much higher concentration of Factor IX than is present in whole plasma or serum. This use of a concentrated antigen source may account for the high hemagglutination titers which were observed.

The rise in inhibitor concentration 6 to 7 days after transfusions of Factor VIII rich plasma or fractions is compatible with an anamnestic response and adds further support to the concept that the inhibitor is an antibody. The recent demonstration that a rabbit antibody to canine Factor VIII progressively inactivates Factor VIII at 28 C. in a manner closely analogous to that of the human inhibitors41,42 adds credence to the antibody hypothesis. One could postulate, therefore, that the Factor VIII in normal plasma, when transfused into patients with hemophilia A, acts as a foreign protein and evokes an antibody response.

This study demonstrates the usefulness of a simple and versatile test, the PTT, in detecting the inhibitor which may develop in patients with hemophilia A. When used to determine the anticoagulant titer of a given plasma sample, the PTT provides a useful laboratory test for determining the type of therapy for hemophilic patients with an inhibitor. If the anticoagulant titer is initially undetectable or very low—i.e., 1:2–1:4 after 60 minutes incubation—plasma therapy may be of benefit. A higher anticoagulant titer appears to render plasma therapy useless because Factor VIII in normal plasma is neutralized before it can attain hemostatic levels or before it reaches the site where hemostasis is needed.

Other authors have demonstrated that most of the inhibitors which develop in patients with hemophilia A act specifically against Factor VIII.9,17,20,43 This is further documented by our observations that such inhibitors injected into
dogs produce a transient hemophilic state which is similar from a laboratory standpoint to canine hemophilia originally described by Graham and associates.44 Our observations confirm the previous brief report of Shulman and coworkers45 that the Factor VIII inhibitor acts similarly in vitro and in vivo. This study also demonstrates the cross-reactivity of human anti-Factor VIII with canine Factor VIII. Cross-reactivity of the inhibitor with porcine Factor VIII might occur too, inasmuch as the intravenous administration of the latter temporarily decreased the inhibitor titer of patient B. H.

The exchange transfusion was thought to be lifesaving in this patient even though others have apparently not had the same good results.46 Even though inhibitor activity could still be detected after incubation, it appeared that Factor VIII inhibition was sufficiently slow to permit effective hemostasis. This experience suggests that exchange transfusions may be an effective means of treating serious hemorrhage in hemophilic patients with circulating anticoagulants, a conclusion in agreement with that of McMillan and coworkers.47 However, it should be emphasized that there are two obvious hazards of exchange transfusion—namely, an increased risk of homologous serum hepatitis and a marked increase in anticoagulant titer. Our patient developed the latter, but during frequent observations one year after the exchange transfusion, he had no clinical or chemical evidence of hepatitis. The very potent porcine Factor VIII fractions were only transiently effective according to in vitro tests, but even a transient effect may have been sufficient to maintain hemostasis.

**Summary**

Factor VIII inhibitors which developed in four patients with hemophilia A are described. These inhibitors are apparently specific for Factor VIII and are capable of inducing a transient hemophilic state when injected into dogs. The genesis, properties, and mode of action of these inhibitors can be explained on an immunologic basis and it seems most likely that they represent an antibody to Factor VIII. One hemophilia A patient, with retroperitoneal hematoma and a potent Factor VIII inhibitor, was successfully treated by an exchange transfusion followed by administration of purified porcine Factor VIII.

**Summario in Interlingua**

Es describite inhibitore de Factor VIII le quales se disveloppava in quatro patientes con hemophilia A. Il pare que iste inhibitores es specific pro Factor VIII e que illos possede le capacitate de inducer un transcitente stato hemophilic quando illos es injicite ad in canes. Le genese, le proprietates, e le modo de action de iste inhibitores pote esser explicate immunologicamente, e il pare le plus probable que illos representa un anticorpore anti Factor VIII. Un del patientes con hemophilia A, con hematoma retroperitonee e un potente inhibitor de Factor VIII, esseva tractate a bon successo per medio de un transfusion de excambio sequite del administration de purificate Factor VIII porcin.
ACKNOWLEDGMENT

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