Combined Hemophilia and PTC Deficiency

By J. M. Hill and Robert J. Speer

Since Otto described the disease in 1803, hemophilia has been recognized primarily as a clinical entity. A severe bleeding tendency especially associated with joint and deep tissue hemorrhage, a failure or delay in clot formation, and a family history of sex-linked inheritance characterized a distinct clinical picture. Many investigators have studied this disease in an effort to ascertain the nature of the obvious blood coagulation defect. In the course of these investigations, almost every factor known to be important in coagulation has been presumed to be abnormal in hemophilia; however, history has proven most of these claims baseless.

The original observations by Addis that a small amount of normal plasma or a crude globulin fraction derived from it was capable of completely correcting the hemophilic coagulation defect in vitro was not fully appreciated until confirmed by other workers some twenty-five years later. Subsequently, it was demonstrated that some substance, other than fibrinogen, in Cohn Fraction I could be employed for this purpose. It was also established that hemophilic plasma did not contain this globulin in normal amounts. As a result, it was commonly accepted that the etiology of hemophilia had been established and that the disease was characterized simply by an inherent deficiency of so-called antihemophilic globulin.

In 1947, however, Pavlovsky reported that the blood or plasma from certain hemophiliacs was capable of correcting the coagulation defect in the blood of another patient having the same clinical disease. This finding strongly implied that more than a single coagulation defect was involved. Further, the studies by Hill and co-workers on the inheritance of apparently typical hemophilia gave results suggestive of multiple factors in the causation of this disease.

Aggeler and co-workers in 1952, demonstrated very conclusively that the deficiency of a second thromboplastic factor, plasma thromboplastin component (PTC) could result in a hemorrhagic condition clinically indistinguishable from hemophilia. In the same year, Biggs and co-workers, as well as Schulman and Smith, reported cases apparently suffering from a deficiency of this factor.

Recently, Rosenthal and his collaborators have called attention to a third factor which they term plasma thromboplastin antecedent (PTA). Deficiency of this thromboplastic factor led to a condition that presented some clinical features differing slightly from classical hemophilia in the cases described. A family with several members showing both clinical and laboratory findings indicative of PTA-deficiency has recently been studied in our laboratory in comparison with the cases reported in this paper.

In contrast with the thromboplastic deficiency conditions described above,
COMBINED HEMOPHILIA AND PTC DEFICIENCY

Tocantins and others have postulated the existence of excess antithromboplastin or an excess heparin-like anticoagulant as the basic cause of coagulation failure or delay in hemophilia.

Other hemophilia-like diseases, not related to thromboplastic deficiencies, have been described. Owren and Seegers have described an accelerator of prothrombin conversion (plasma accelerator globulin), a deficiency of which results in a hemorrhagic disease simulating hemophilia in many respects. Deficiency of a second prothrombin conversion accelerator, proconvertin (Owren), or serum prothrombin conversion accelerator precursor (Alexander), apparently may also lead to hemophilia-like conditions.

The present paper is intended as a preliminary report on two patients, originally diagnosed and treated as classical hemophiliacs, who appear on closer laboratory examination, to suffer from a combined deficiency of both AHG and PTC. The combined deficiency was revealed only in a re-study with newer technics of a family previously reported.

CASE REPORT

The two patients considered in this study were brothers, J. B., age seven, and B. B., age five. J. B. was first seen in September, 1947, when he was one year old. He presented a history of severe bleeding from earliest infancy, having bled for five days after circumcision. He also had multiple large hematomas following trivial bruises as a baby. During many subsequent episodes, the patient suffered from hemorrhage into joints and into muscles and along deep fascial planes often not associated with known injury. He bled severely after biting his tongue and required transfusion of fresh blood and antihemophilic globulin. On one occasion while suffering from tonsillitis, there was sufficient diffuse hemorrhage in the neck tissues to embarrass respiration. The brother, B. B., was essentially identical with respect to history, clinical and laboratory findings.

The family history revealed no other cases of clinical hemophilia. However, there were few male progeny in the four generations on whom information was available.

The laboratory studies over a period of years consistently showed normal platelet counts, bleeding time, prothrombin, accelerator globulin, and proconvertin. Studies of bone marrow and peripheral blood were normal except when the red cell level was depressed after hemorrhage.

Significant positive laboratory findings initially consisted of a marked prothrombin utilization defect (40% utilized at 24 hours) and a prolonged clotting time by the Lee and White method during period of hemorrhage.

Therapy with fresh blood and commercial antihemophilic globulin was effective in controlling hemorrhage and in reducing clotting times. Later, frozen plasma prepared from freshly drawn blood was used successfully to control the hemorrhagic tendency for periods of several months.

Recently, both patients have been studied with many of the newer laboratory technics. Both have shown a marked prothrombin utilization defect by the method of White, Aegger, and Glendening. This prothrombin utilization test was repeated with three variations: (1) with added Cohn Fraction I as a source of AHG; (2) with added normal prothrombin-free serum as a source of PTC; and (3) with the simultaneous addition of both AHG and PTC as given in (1) and (2) above. During the periods of hemorrhagic crisis, both patients were essentially identical by these tests. However, they differed distinctly from patients deficient solely in AHG or in PTC. The results of these tests are presented in table 1.

According to this method, 2.0 ml. of oxalated whole blood (free of tissue thromboplastin by clean venipuncture) was mixed gently with 0.1 ml. of saline or an equal volume of an appropriate corrective reagent, and the mixture incubated at 37 C. for one hour. At the end of this period, the reaction was stopped by introducing a predetermined amount of sodium oxalate, mixing, and centrifuging. Prothrombin in the supernatant "serum" and in a sample
Table 1.—Prothrombin Utilization Tests for Differential Diagnosis in Hemophilia-like Diseases

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>AHG* added (Cohn I)</th>
<th>PTC added (serum)</th>
<th>AHG &amp; PTC added</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHG deficiency, classical hemophilia</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>PTC deficiency</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PTA deficiency</td>
<td>-</td>
<td>+</td>
<td>+†</td>
<td>+†</td>
</tr>
<tr>
<td>Combined AHG &amp; PTC deficiency (unreported)</td>
<td>-</td>
<td>±</td>
<td>±</td>
<td>+</td>
</tr>
</tbody>
</table>

Patients in hemorrhagic crisis

| B. B.                         | -       | ±                   | ±                 | +               |
| J. B.                         | -       | ±                   | ±                 | +               |

Patients in clinical remission

| B. B.                         | -       | ±                   | ±                 | +               |
| J. B.                         | -       | +                   | ±                 | +               |

- = Less than 5% utilization of prothrombin.
± = Partial utilization of prothrombin.
+ = More than 70% utilization of prothrombin.
* Commercial Cohn Fraction I, as well as partially purified AHG tested.
† Normal serum reported to contain PTA as well as PTC.

of the patient's oxalated plasma was assayed by Owren's technic. Prothrombin utilization, in per cent, was calculated as: (Plasma Prothrombin – "Serum" Prothrombin/Plasma Prothrombin) × 100. In this laboratory, the normal prothrombin utilization was found to be 70–100 per cent. In table 1, the term, “Partial utilization,” is employed to designate prothrombin utilization of 10–40 per cent.

The corrective reagents employed in the prothrombin utilization tests were: (1) Commercial Cohn Fraction I, Cutter Laboratories, as a source of AHG. It was always freshly prepared from the lyophilized solid as a 10 per cent aqueous solution just prior to use. (2) AHG concentrate, purified in this laboratory by a combination of previously published adsorption and salting-out techniques. As in 1) above, this material was retained in the form of the lyophilized solid until just prior to use, when a 10 per cent aqueous solution was prepared. (3) Aged serum was obtained from healthy, normal donors, and was allowed to stand for 48 hours at room temperature before use. It was then tested, as described below, and if found satisfactory, was frozen and stored at -20 C. until ready for use. All corrective reagents were checked for “purity” and potency by employing them in the prothrombin utilization tests, as described, against blood samples of well-characterized AHG- and/or PTC-deficient patients. Under such conditions, (1) and (2) were capable of routinely correcting the prothrombin utilization defect of a typical AHG-deficient hemophiliac from less than 5 per cent to well above 70 per cent (usually greater than 95 per cent) without altering the prothrombin utilization of a PTC-deficient patient. On the other hand, aged serum (3) was able to increase the prothrombin utilization of PTC-deficient patients from 5-10 per cent to 70–100 per cent without improving that of the AHG-hemophilia. All three reagents have been found to provide complete correction for PTA-deficient patients studied in this laboratory, and BaSO₄-adsorbed, aged serum has been employed as a differential reagent in these cases.

In addition to the laboratory tests described in table 1, a large variety of additional studies have been undertaken on these patients. These results have served only to exclude other possible hemorrhagic conditions, and did not aid appreciably in the differential diagnosis.

Discussion

Table 1 presents the experimental results observed in the case of J. B. and B. B. during a period of hemorrhagic crisis, as well as during clinical remission.
induced by therapy. It summarizes, as well, the results which one observes when other conditions of plasma thromboplastic deficiency are studied under these conditions. The findings are quite distinct and different in the various hemophilia-like diseases. In fact, the prothrombin utilization test, modified by the separate addition of various corrective components, is of considerable differential diagnostic value in such situations. Patients illustrating each of these defects have been studied comparatively in this laboratory, with the results shown. The findings in the present case appear to be completely consistent only with the combined deficiency of antihemophilic globulin and plasma thromboplastin component.

Single deficiencies of AHG or PTC are excluded by the inadequacy of Cohn Fraction I or normal serum in providing in vitro correction when employed separately. Plasma thromboplastin antecedent, as described by Rosenthal, cannot be as rigorously excluded on the basis of the present data, since this author found that normal serum served as an adequate source of both PTC and PTA. However, the very fact that both J. B. and B. B. showed very slight correction with normal serum alone when in a condition of clinical crisis, seems to militate against this conclusion. The presence or absence of excessive antithromboplastin is impossible to prove with these tests alone. This is particularly true if one assumes that the antithromboplastin is non-specific and inhibits equally any intrinsic thromboplastin, regardless of its origin from AHG, PTC, or PTA.

Accordingly, the evidence seems to point very strongly to a combined deficiency of both antihemophilic globulin and plasma thromboplastin component. Not only do the laboratory data favor such a postulate, but the family history, the clinical symptomatology, and effectiveness of transfusion therapy are compatible with this conclusion. Additional coagulation studies on both patients and relatives are currently under way.

SUMARIO IN INTERLINGUA

Es reportate prebiminarimente le casos de duo fratres, originalmente diagnosticate e tractate como hemophilos classic, sed qui—post plus exacte examines laboratorial—pare sufrer del combination de deficientias de si ben globulina anti-hemophilic etiam de componente thromboplastina plasmatic. Iste postulado es supportate etiam per le historia del familia, le symptomatologia clinica, e le efficacia del therapia a transfusiones. Ambe patientes e altere membros de lor familia va esser subjecite a studios additional de coagulation.

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