Synthesis of AHF in von Willebrand's Disease

By Jessica H. Lewis

A HEMORRHAGIC DISEASE, first described by von Willebrand in 19261 in a large family living on the Aland Islands, has gone through a fascinating diagnostic metamorphosis. Initially it was thought to be due to a platelet abnormality,2,3 later to a vascular abnormality;4,5 more recently, to lack of a plasma factor(s).6,7 This changing pathogenetic view reflects not only increasing diagnostic skill but also inclusion in some publications of patients with varying hemostatic defects. In 1957, Nilsson and co-workers7 studied 15 members of the original family on the Aland Islands and found mild AHF (factor VIII) deficiency in all bleeders and prolonged bleeding times in those with moderate to severe hemorrhagic symptoms. Other tests, including those of platelet function, were normal. In one patient the prolonged bleeding time was corrected by an infusion of plasma fraction I-O. Thus it seemed possible to re-define von Willebrand’s disease as a hemorrhagic disorder, usually familial, characterized by a prolonged bleeding time and a low level of AHF. With this definition in mind, descriptions of many similar cases can be found in the literature including those in which the disease has been called “vascular hemophilia,” “pseudohemophilia B” and “angiohemophilia A.”

The patient presented herewith appears to fall within the definition of von Willebrand’s disease although she lacks a positive family history. Of particular importance is the apparent ability of this patient to synthesize her own AHF when infused with normal or hemophilic plasma.

METHODS

The methods used in this investigation have been published previously.8,9

Case History

V. F., a 5 year old Caucasian girl born in August 1958, has been studied in our laboratory on three occasions. Easy and frequent bruising, bleeding from small cuts and from eruption of teeth, hematoma in the muscles of the legs, and epistaxis have been almost constant complaints since infancy. At age 2, permanent loss of vision in the right eye followed minor injury and retinal hemorrhage. She has received many plasma transfusions which usually have excellent therapeutic effects.

The family history is shown in figure 1. The mother and maternal grandmother described occasional easily controlled nosebleeds; otherwise, no other member of the family has shown any bleeding tendency. Coagulation studies carried out on family members 1–4 showed no abnormalities.

Laboratory studies on V. F. are shown in table 1. The initial bleeding time, at age of

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Supported in part by research grants from the National Health Institutes, United States Public Health Service (HE-02254 and HE-03036), and from the Pittsburgh Health Research and Services Foundation (A-48).

Submitted June 6, 1963; accepted for publication July 20, 1963.

Blood, Vol. 23, No. 2 (February), 1964
10 months, was normal, but all subsequent determinations, including those performed by other physicians, have been prolonged. The tourniquet test was markedly positive on one occasion. Clotting times were normal in glass but prolonged in silicone. Prothrombin consumption was within normal limits (86-99 per cent), but serum prothrombin time was consistently abnormal (normal = > 20 seconds). Assays for all coagulation factors except AHF were normal as were platelet count and platelet thromboplastic factor. AHF (factor VIII) assayed at 10 to 15 per cent of normal.

Capillary microscopy was unsatisfactory.

RESULTS

Effects of Plasma Transfusions

Normal and hemophilic (AHF = 0) plasmas, each preserved fresh-frozen in plastic bags (Fenwal), were administered 6 days apart.

Figure 2 illustrates the marked shortening in bleeding time (Duke) observed 1 hour following both infusions. This effect was fleeting, only a minor shortening being still detectable 4 hours after the hemophilic plasma. On the other hand, the AHF level increased gradually, reaching over 70 per cent of normal by 4 hours. At 24 hours the levels were still high (60-65 per cent). The anticipated rise in AHF level following the hemophilic plasma infusion was zero, while that following the normal plasma was 13 per cent. (Blood volume was calculated as 9 per cent of body weight (14.3 Kg.)

Corresponding changes in thromboplastin generation are shown in figure 3. At each time the test was carried out using normal platelets and serum and the patient's barium sulfate-treated plasma. Following the normal plasma infusion, the amount of thromboplastin generated increased, reaching normal levels at 4 hours. Following the hemophilic plasma infusion, the amount of thromboplastin generated also increased. Unfortunately, at 4 hours the normal TGT mixture did not reach the usual substrate clotting time of 10 seconds. V. F.'s plasma at 4 hours reacted similarly to the normal plasma.
AHF IN VON WILLEBRAND'S DISEASE

Table 1—Coagulation Studies on Patient V. F.

<table>
<thead>
<tr>
<th></th>
<th>1959</th>
<th>1961</th>
<th>1963</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding time (min.)</td>
<td>3</td>
<td>10+</td>
<td>10+</td>
</tr>
<tr>
<td>Tourniquet test</td>
<td></td>
<td>4+</td>
<td></td>
</tr>
<tr>
<td>Clotting time—glass (min.)</td>
<td>9</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Clot retraction</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Silicone (min.)</td>
<td>52</td>
<td>150</td>
<td>120</td>
</tr>
<tr>
<td>Prothrombin consumption (%)</td>
<td>86</td>
<td>89</td>
<td>87</td>
</tr>
<tr>
<td>Serum prothrombin time (sec.)</td>
<td>18.3</td>
<td>18.8</td>
<td>18.8</td>
</tr>
<tr>
<td>Quick prothrombin time</td>
<td>100</td>
<td>94</td>
<td>79</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>90</td>
<td>100</td>
<td>101</td>
</tr>
<tr>
<td>Factors VII &amp; X</td>
<td>98</td>
<td>78</td>
<td>61</td>
</tr>
<tr>
<td>Proaccelerin %</td>
<td>96</td>
<td>136</td>
<td>100</td>
</tr>
<tr>
<td>AHF normal</td>
<td>10</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>PTC</td>
<td></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>85</td>
<td>120</td>
<td>—</td>
</tr>
<tr>
<td>Platelet thromboplastic factor</td>
<td></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Platelet count (per cu. mm.)</td>
<td>466,000</td>
<td>342,000</td>
<td>394,000</td>
</tr>
</tbody>
</table>

DISCUSSION

In our patient, normal and hemophilic plasmas were equally effective in correcting the prolonged bleeding time and in producing a subsequent rise in AHF level. The gradual rise in AHF can be interpreted in two ways: (1) some factor is supplied which allows the patient to synthesize her own AHF or, (2) excessive destruction of AHF is prevented. The latter theory derives from a suggestion by Biggs and Macfarlane. It is that a widespread capillary defect might cause increased consumption of factor VIII. The very brief effect of plasma infusion on bleeding time and the continued rise in AHF after the bleeding time reverts argue against this possibility. Thus it seems probable that the von Willebrand's patient is capable of synthesizing factor VIII when presented with an appropriate material which circulates in normal and hemophilic subjects.

Nilsson and co-workers have shown a correction of the prolonged bleeding time by fraction I-0 prepared from normal or hemophilic plasma but not from the plasma of patients suffering from von Willebrand's disease. These authors also show that the V. W. factor is distinct from AHF and fibrinogen (both present in fraction I-0) and stress the importance of silicone technic in its preservation. This observation may be important in explaining the lack of corrective effect on bleeding time of fraction I (prepared from plasma exposed to glass) described by McMillan et al. Borchgrevink et al. noted that the corrective effect upon bleeding time was highly dependent upon the method employed, the Duke bleeding time being consistently shortened while the Ivy showed little or no response.

The effects of transfusions of hemophilic plasma in von Willibrand's disease have been studied by a number of workers. All agree that the bleeding time is shortened, although briefly and not necessarily to normal.
changes in AHF level have varied from no change,15 no change as judged by prothrombin consumption tests,16 to the gradual and sustained increase found by Nilsson et al., Cornu and co-workers,17–20 Borchgrevink et al.13 and, very recently, by Biggs and Matthews.14 The present report confirms these observations. The gradual rise in AHF concentration is in marked contrast to the oft-repeated studies of the effects of transfusions in hemophilia, in which the AHF rises abruptly to levels not above those anticipated, subsequently falling rapidly with an estimated circulatory half-life of 4 hours (or less).

These observations suggest the possibility that factor VIII deficiency in hemophilia is related to a genetically controlled abnormality late in the cellular processes involved in AHF synthesis, while that in von Willebrand’s disease is related to lack of another factor which functions earlier in this series of reactions. McLester and Graham21 suggest two genetic models either of which might be used to explain the interrelationships between hemophilia and von Willebrand’s disease. The elucidation of these reactions and their relationship to the control of bleeding time await the researcher with adequate and available clinical material.

**SUMMARY**

A 5 year old girl suffering from a severe hemorrhagic disorder which appears identical to von Willebrand’s disease is presented. Transfusion of either normal or hemophilic plasma resulted in brief shortening of the bleeding time and gradual and sustained elevation of the AHF (factor VIII) level. The latter observation suggested that this patient was able to synthesize her
AHF IN VON WILLEBRAND'S DISEASE

Fig. 3.—Effects of transfusions of normal or hemophilic plasma on TGT assay of BaSO₄-treated plasma.

own AHF when infused with a material present in normal or hemophilic plasma.

SUMMARIO IN INTERLINGUA

Es presentate le caso de un puera de 5 annos de etate suffrente de un sever disordine hemorrhagic que pare esser identic con morbo de von Willebrand. Le transfusion de normal o etiam de hemophilic plasma resultava in breve reductiones del tempore de sanguination e in un gradual e sustenite elevation del nivellos de factor antihemolytic (factor VIII). Iste secunde constatation suggereva que iste patiente habeva le capacitate de synthetisar su proprie factor antihemolytic quando illa recipeva infusiones de un material que es presente in plasma normal como etiam in plasma hemophilic.

ACKNOWLEDGMENT

We express our gratitude to Dr. Paul Gaffney, Professor of Pediatrics, University of Pittsburgh, for referring this patient, and for encouragement in the study of this disease.

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