ANALYTIC REVIEW

Von Willebrand’s Disease—Diagnostic Criteria

By Harvey J. Weiss

In 1926, and later in 1931, von Willebrand described an autosomal bleeding disorder in several families living in the Aland Islands in which the most significant abnormality was a prolonged bleeding time.1 Studies by Jürgens et al.2 and Nilsson and co-workers3 in 1957 disclosed that many of these Aland patients also had a deficiency of antihemophilic globulin (AHG), thereby indicating their similarity to patients reported from other countries during the preceding 5 years.4-8 In the present review the term “classic von Willebrand’s disease” will be used to describe an inherited autosomal bleeding disorder in which the dual defects of a prolonged bleeding time and a decrease in AHG are found. The underlying defect in hemostasis is not known. In patients whose AHG values are less than 35 per cent, retarded coagulation may play a role; AHG values of 35–50 per cent, although lower than normal, are probably of lesser significance. The cause of the prolonged bleeding time has been variously attributed to abnormal platelets or capillaries and lack of a second plasma factor, distinct from AHG. Finally, the disease may be present in some patients in whom either AHG, the bleeding time, or both, are normal. This is evident from studies on families in whom some members showed the dual abnormalities while other clinically affected relatives did not.9,10 The diagnosis of von Willebrand’s disease may be particularly difficult in patients who do not show the dual abnormality and in whom family studies are either negative or not available. Attempts have been made, therefore, to develop other diagnostic criteria. Quick has reported that patients with von Willebrand’s disease are more likely to have their bleeding time prolonged by aspirin ingestion than are normal subjects and has proposed an “aspirin tolerance test” as an aid to the diagnosis.11,12 Other investigators have found platelet function tests and the response to plasma fractions useful. The difficulties entailed in both performing and interpreting the various tests used to diagnose the disorder are reviewed herein. The historical aspects have recently been the subject of extensive reviews.13,14

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Bleeding Time and AHG Abnormalities

The findings of a prolonged bleeding time and decreased AHG value established the diagnosis of von Willbrand's disease, particularly if an autosomal type of inheritance can also be elicited. Several technics have been used to determine the bleeding time, which may show wide daily variations for each patient. With each method, the results will be influenced by the sharpness of the blade and the angle between its cutting edge and the skin, the depth and width of incision and the skin thickness. Using the Duke method (earlobe puncture), Blatrix and Corredor reported a mean value of 2.5 minutes and a range of 1.5 to 4.5 minutes in 100 normal subjects, while Adelson and Crosby reported values of 4.54 ± 3.76 (2S.D.) minutes in 138 subjects. With the Ivy method (forearm puncture wound), Blatrix and Corredor reported a mean value of 4.5 and range of 2.5 to 8.5 minutes; in our laboratory, the mean value in 30 normal subjects was 3.4 ± 2.2 (2S.D.) minutes, obtained on puncture wounds of 3 mm. depth made with a number 11 Bard Parker blade. Borchgrevink has introduced a modification of the standard Ivy method in which the puncture-type wound is replaced by a transverse incision, 6 mm. long and 1 mm. deep. He and his co-workers found this modified Ivy technic to be more sensitive than the Duke method for detecting abnormalities in von Willebrand's disease. There is no information, however, on how it compares with the standard Ivy method.

AHG is assayed by determining the corrective effect of the test plasma on the clotting abnormality of a substrate deficient in AHG. The clotting tests used most frequently for the assay are modifications of either the partial thromboplastin time or the thromboplastin generation test. The clotting time obtained with the test plasma is compared with that of pooled normal plasma and the result converted to per cent of normal activity from a curve obtained by performing the assay on serial dilutions of the control plasma. The result obtained assumes that the control plasma is representative of the population mean. The validity of this assumption and the difficulties entailed in reproducing the results from day to day are discussed in detail elsewhere. The usual normal values are stated to be 50-200 per cent.

Platelet Defects

Von Willebrand and Jürgens attributed the defect in hemostasis in their Aland patients to defective platelets and for many years the condition was known as von Willebrand-Jürgens thrombocytopathia, particularly in the European literature. Their conclusions were based on early studies using a "capillary thrombometer" and, later, on the findings that platelet clotting activity (platelet factor 3), assayed by testing washed platelets in the thromboplastin generation test, was abnormal. However, other investigators, using the same method, have found normal platelet factor 3 (PF-3) activity in patients with classic von Willebrand's disease. Morphologic abnormalities, detected by electron microscopy, have been reported by several investigators. During the past 10 years, the mechanisms by which platelets contribute to
hemostasis have been extensively studied and new technics for testing platelet function have been developed. Injury to a blood vessel is followed by rapid adhesion of platelets to denuded connective tissue. The mechanism is unknown but may be electrostatic in nature. In von Willebrand's disease, the platelets appear to have a normal surface charge, as determined by electrophoretic mobility measurements, and they adhere normally to injured connective tissue. Following adhesion, platelets release adenosine diphosphate (ADP), which results in their aggregation and contributes to activation of their clot promoting activity (PF-3). These reactions may be studied in vitro by incubating citrated platelet-rich plasma with agents such as kaolin, connective tissue fragments or collagen. When tested in this manner, 8 patients with classic von Willebrand's disease showed normal platelet aggregation, ADP release and PF-3 activity, in contrast to the abnormal results obtained in 6 patients with normal AHG values whose disorder we have called thrombopathia (See Discussion).

Although platelet aggregation is normal in von Willebrand's disease, Vainer and Caen have described an unexplained effect which occurs when ADP, in a concentration of 0.05 µg. per 0.8 ml., is added to citrated platelet-rich plasma. In von Willebrand's disease, and not in normal subjects, these authors observed an immediate increase in optical density (with platelet aggregation, a decrease occurs) and suggested that this photometric test might be diagnostically useful. Exceptions, however, were found. We have tested only two patients with classic von Willebrand's disease by this technic and did not observe any increase in optical density.

The abnormality which has been most frequently reported in von Willebrand's disease is a relative nonadherence of the platelets to glass surfaces. Three methods, with variations, have been used to study platelet adhesiveness in this disorder. In the H. P. Wright test, anticoagulated blood is rotated in a glass vessel for 20–80 minutes and the percentage of platelets which adhere to the glass is determined. With this method, normal values for platelet adhesiveness have been reported in von Willebrand's disease. In 1964, Ødegaard and co-workers, modifying Hellem's original method, determined platelet adhesiveness by filtering platelet-rich plasma through glass beads in the presence of varying amounts of ADP. They reported that abnormally low values were obtained in von Willebrand's disease, but only if the concentration of ADP was 0.05 µg. per ml. of PRP. Cronberg et al. and Weiss, however, obtained normal results with this technic in similar patients. A third method was introduced by Salzman, who filtered venous blood directly through glass beads into a Vacutainer tube and found decreased platelet adhesiveness in patients with von Willebrand's disease. The results were confirmed by Strauss and Bloom and by Meyer and co-workers. Zucker filtered citrated blood rapidly through beads and also found decreased adhesiveness in von Willebrand's disease; however, she was not able to reproduce the results using a different batch of beads. Negative results have been reported by other investigators. In our experience, when platelet adhesiveness was determined by Salzman's original technic, low
Table 1.—Patients With von Willebrand’s Disease

<table>
<thead>
<tr>
<th>No.</th>
<th>Ivy Bleeding Time (Min.)</th>
<th>Ivy AHG (%)</th>
<th>Modified Salzman (%)</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Mean</td>
<td>30</td>
<td>60</td>
<td>97.3*</td>
<td>56.3</td>
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<tr>
<td>Subjects S.D.</td>
<td>3.4</td>
<td>1.1</td>
<td>1.2-5.6</td>
<td>49-194*</td>
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<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Ivy Bleeding Time (Min.)</th>
<th>Ivy AHG (%)</th>
<th>Modified Salzman (%)</th>
<th>Inheritance</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>F</td>
<td>&gt;30, &gt;30, &gt;30†</td>
<td>15</td>
<td>N.D.†</td>
<td>Sporadic</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>F</td>
<td>&gt;30, &gt;30, &gt;30</td>
<td>5</td>
<td>5</td>
<td>Sporadic</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>F</td>
<td>&gt;20, &gt;20, &gt;20</td>
<td>30</td>
<td>2</td>
<td>Autosomal</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>F</td>
<td>&gt;30, &gt;30, &gt;30</td>
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<td>Sporadic</td>
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<tr>
<td>5</td>
<td>42</td>
<td>F</td>
<td>&gt;15</td>
<td>8</td>
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</tr>
<tr>
<td>6</td>
<td>13</td>
<td>F</td>
<td>7</td>
<td>7</td>
<td>N.D.</td>
<td>Daughter</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>M</td>
<td>10, &gt;15</td>
<td>8</td>
<td>39</td>
<td>Son</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>M</td>
<td>9</td>
<td>9</td>
<td>61</td>
<td>Son</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>F</td>
<td>N.D.</td>
<td>40</td>
<td>—</td>
<td>Grandmother</td>
</tr>
<tr>
<td>10</td>
<td>35</td>
<td>M</td>
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<td>14</td>
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<td>35</td>
<td>12</td>
<td>Grandson</td>
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<tr>
<td>12</td>
<td>10</td>
<td>F</td>
<td>9</td>
<td>50</td>
<td>34</td>
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</tr>
<tr>
<td>13</td>
<td>21</td>
<td>F</td>
<td>10</td>
<td>33</td>
<td>N.D.</td>
<td>Autosomal</td>
</tr>
<tr>
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<td>40</td>
<td>F</td>
<td>25</td>
<td>28</td>
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<td>F</td>
<td>8,8</td>
<td>31</td>
<td>29</td>
<td>Sporadic</td>
</tr>
<tr>
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<td>25</td>
<td>M</td>
<td>&gt;30, &gt;30</td>
<td>2</td>
<td>27</td>
<td>Sporadic</td>
</tr>
<tr>
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<td>23</td>
<td>F</td>
<td>4,4</td>
<td>29</td>
<td>11</td>
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<td>22</td>
<td>F</td>
<td>11,6,10</td>
<td>40</td>
<td>8</td>
<td>Autosomal</td>
</tr>
</tbody>
</table>

*Values presented elsewhere67 converted to log AHG68 and statistics recalculated.
†Bleeding times (average of 2 determinations) performed on different days.
‡N.D., not determined.

Patients 5-8 and 9-11 are from two separate families; all others are unrelated.

Values were obtained in many normal subjects. More satisfactory results were obtained by using a mechanical pump to regulate the flow rate through the beads. With this modified method, values for platelet adhesiveness were clearly abnormal in 6 out of 8 patients with classic von Willebrand’s disease.34 We have now performed the test in 14 patients; the results were abnormal in 11, normal in 2 and borderline in 1 (Table 1). O’Brien and Heywood, using heparinized blood, have also emphasized the critical importance of the flow rate, as well as the filter length, in obtaining satisfactory results.45 They used 2 flow rates and obtained low values in von Willebrand’s disease only with the more rapid rate. Thus, in their studies, normal values were obtained in von Willebrand patients when the flow rate was too slow, while in our studies low values were obtained in normal subjects when the rate was too rapid. The mechanism of the platelet-glass interaction and the physiologic relevance of the abnormal adhesiveness in von Willebrand’s disease remains to be determined. A more detailed discussion of platelet adhesiveness tests, and their
significance in other disorders, may be found in the recent review of Hartmann.46

Plasma Defects

When patients with classical von Willebrand’s disease are transfused with plasma, serum or fraction I from normal subjects or, even more dramatically, from hemophiliacs, an increase in AHG occurs, maximum at 4–24 hours, which is greater than would be expected from its concentration in the infusate.47,48 This observation, which was first reported by Nilsson and co-workers,6 suggests that patients with von Willebrand’s disease lack a plasma factor, present in normal subjects and hemophiliacs, which is necessary for AHG synthesis. By contrast, AHG synthesis does not occur in hemophiliacs who are transfused with von Willebrand or with normal plasma.9 The plasma infusion test may, therefore, be useful in establishing a diagnosis of von Willebrand’s disease or mild hemophilia in a patient with moderate AHG deficiency and a normal bleeding time.

Nilsson and co-workers also reported that transfusion of normal or hemophiliac fraction I and plasma often shortened the Duke bleeding time in patients with classical von Willebrand’s disease.6 This has been confirmed by other investigators47,49 and, when observed, may be helpful in establishing the diagnosis. It has not been reported, to my knowledge, in any condition which is clearly not von Willebrand’s disease. Negative results are less significant. The plasma “antibleeding” factor is labile and must be given in large amounts.6–49 Fraction I preparations prepared in different laboratories vary in their potency.48 Perkins has reported that the “antibleeding” factor is present in cryoprecipitate.50 It is sometimes stated that a shortening of the bleeding time is more easily obtained using the Duke method than with the Ivy method.18–51 It should be emphasized that in most of these reports, the Ivy bleeding time was determined by Borchgrevink’s modification (vide supra). In our experience, when the Duke bleeding time was shortened, the standard Ivy bleeding time also decreased.49

The relationship between the AHG stimulating factor and the “antibleeding” factor is not clear. Although the stimulating factor has been found in plasma and serum fractions which do not shorten the bleeding time,6,48 it has not been definitely established that the two factors are completely different substances.

Effect of Aspirin

Quick has recently proposed that the response to aspirin ingestion may be useful in diagnosing von Willebrand’s disease in patients in whom the diagnosis may be difficult by other criteria.11,12 Confirming previous observations,52 he noted that aspirin, in a dosage of 1.2 g, often prolongs the bleeding time in normal subjects while sodium salicylate has no effect. In 50 patients with undiagnosed, mild bleeding disorders this often occurred with a dosage of 0.6 Gm. AHG was decreased in 2 of the 5 subjects in whom it was assayed. Quick has suggested that all of the patients have von Willebrand’s disease
and has postulated that the effect of aspirin may be to further decrease the plasma "antibleeding" factor. Recent studies suggest a different mechanism. Ingestion of aspirin, in both high and relatively low doses, by normal subjects resulted in decreased platelet aggregation by connective tissue due to impairment in the release of platelet ADP. This abnormality in the platelet-connective tissue reaction is similar to the findings in patients with thrombopathia (see Discussion) and is quite unlike the normal results obtained in patients with classic von Willebrand's disease. Further evidence supports the hypothesis that aspirin inhibits the platelet release reaction. When citrated platelet-rich plasma is stirred with either adrenaline or critical concentrations of ADP at 37 C., aggregation occurs in two waves, the first caused by the agent added, the second by ADP released from the platelets. Aspirin, in vivo and in vitro, inhibits the second, but not the first wave of aggregation, both of which occur normally in von Willebrand's disease. In contrast to the effects of aspirin, sodium salicylate, in comparable dosage, has either no or minimal effects on platelet function. Thus, the abnormalities produced by aspirin do not resemble the findings in von Willebrand's disease and while it may, in addition, decrease the plasma "anti-bleeding" factor, there is no evidence to support this conclusion at the present time. As previously reported by Beaumont and co-workers, aspirin ingestion may accentuate the bleeding tendency in patients with hemostatic defects of various types. We do not believe, however, that a positive "aspirin tolerance test" necessarily indicates a diagnosis of von Willebrand's disease, even when other bleeding disorders appear to have been ruled out by currently available methods.

**DISCUSSION**

From the above, it is clear that the basic abnormality which is responsible for the defect in hemostasis in von Willebrand's disease is unknown. There is no conclusive evidence that the platelets are intrinsically defective. Transfusion of normal platelets does not shorten the bleeding time. Capillary abnormalities are difficult to evaluate because of the wide variation observed in normal subjects. Present evidence indicates that absence of a plasma factor or factors may be responsible for both the prolonged bleeding time and the decreased AHG values which are seen in patients with the classical syndrome. Further characterization of these factors, including a method for their assay, might provide a more direct method for establishing the diagnosis than is now available, particularly in patients in whom either AHG, the bleeding time or both are normal. Since the platelets in von Willebrand's disease are relatively nonadherent to glass, it has been proposed that tests of platelet adhesiveness may be useful in establishing the diagnosis in these difficult cases. The problems involved here are two-fold. First, abnormal results, even in "classic" cases, have not been obtained by all investigators. For reasons outlined earlier, we believe that the failure to detect abnormalities reflect subtle differences in technics. Corroborative studies from several laboratories, as well as those presently being conducted by the International Committee on Hemostasis and Thrombosis, indicate that the
Salzman technic, or modifications of it, will detect abnormal adhesion in many patients with von Willebrand's disease. Unfortunately, in our experience, patients with borderline AHG and bleeding time values may also show borderline values with the Salzman test (Case 12, Table 1 for example). A more fundamental problem is the finding that abnormal results may also be obtained in other patients who appear to differ from von Willebrand's disease by other criteria. We have recently described 6 patients with prolonged bleeding times and normal AHG values in whom the release of platelet ADP was impaired, resulting in decreased PF-3 activation and impaired aggregation by connective tissue. Unlike the findings in Glanzmann's thrombasthenia, primary aggregation by ADP itself was normal. In 4 of these patients with thrombopathia, who appear to have the same disorder as those described independently by Hardisty and Hutton, platelet adhesiveness was abnormal, similar to the findings in von Willebrand's disease. Thus, it is necessary to rule out intrinsic platelet defects in evaluating patients whose Salzman test is abnormal. Platelet studies should include assay of PF-3, measurements of platelet aggregation and ADP release and estimation of clot retraction. In some patients with thrombopathia the serum prothrombin time is abnormal and is corrected by clotting the blood in the presence of a platelet substitute (lipid). In other subjects, the serum prothrombin may be normal. Salzman and Britten and Zucker have reported that normal plasma corrects the abnormal platelet adhesiveness in patients with von Willebrand's disease. These observations, which await more extensive confirmation, again indicate that the platelets are not intrinsically abnormal and suggests that the plasma factor which corrects the bleeding time in vivo may also correct the abnormal platelet adhesiveness to glass. This property could provide an in vitro method for assaying the antibleeding factor.

The decreased AHG values observed in many patients with von Willebrand's disease indicates that the regulation of plasma AHG activity is controlled by at least 2 genes, one of which is on the X-chromosome, abnormal in classic hemophilia, the other on an autosomal chromosome, abnormal in von Willebrand's disease. The paradoxical increase in AHG observed when hemophilic plasma is transfused into a patient with von Willebrand's disease, but not the reverse, has suggested to Graham and co-workers several genetic models for AHG synthesis, including a combining subunit model analogous to hemoglobin. Although "newly synthesized" AHG appears to be similar to normal AHG, as judged by its pH and thermal lability, there is no data to indicate if the pretransfusion AHG is structurally normal. The possibility that the AHG increase is due to decreased destruction, rather than increased synthesis, has not been ruled out. Further knowledge of AHG structure, synthesis and destruction may disclose abnormalities in von Willebrand's disease which will be more helpful, diagnostically, than assay of AHG clotting activity.

**Summary**

Our present criteria for diagnosing von Willebrand's disease are summarized
below and illustrative examples of recently studied patients are shown in Table 1.

A) Prolonged bleeding time and decreased AHG:

When these abnormalities, inherited as an autosomal dominant, are found in several family members, they are considered diagnostic for these patients and for their clinically affected relatives, even though the latter may now show both defects (Case 10). In the absence of family studies, the diagnosis would also be made in individual subjects if a history of bleeding in relatives was consistent with autosomal inheritance (Cases 3,13,18). When family studies are negative (sporadic cases) or no history is attainable, a diagnosis of typical von Willebrand's disease would also be made (Cases 1,2,4,14,15,16) unless intrinsic platelet defects were found (see below) or plasma transfusion failed to produce a progressive increase in AHG activity.

B) Prolonged bleeding time, normal AHG:

The diagnosis would be considered “probable” in such a patient if the following criteria were met:

1. There was no evidence of an “intrinsic” platelet abnormality, as indicated by normal values for platelet aggregation, PF-3 availability and ADP release by connective tissue and kaolin and

2. Platelet adhesiveness, by the modified Salzman test, was abnormal and/or the patient's bleeding time was shortened by transfusion of plasma in a dosage of 13-15 ml. per Kg. body weight.

C) Normal bleeding time, decreased AHG (Case 17):

A diagnosis of probable von Willebrand's disease would be made if:

1. An unequivocal pattern of autosomal dominant inheritance, by history, ruled out hemophilia.

2. The Salzman test was abnormal.

3. Transfusion of hemophilic, as well as normal plasma resulted in a progressive increase in plasma AHG concentration.

D) Normal bleeding time, normal AHG:

The diagnosis would be considered as “possible” if:

1. There was no evidence of intrinsic platelet abnormality (see B 1).

2. The Salzman test was abnormal.

The above criteria are tentative and, undoubtedly, will not satisfy all investigators. To confuse matters even more, some patients who appear to have the “classic” syndrome may also have abnormal platelet factor 38 or fail to “synthesize” AHG after plasma transfusion.13,38 Whether even the “classic” syndrome represents a spectrum of disorders remains to be determined.

SUMMARIO IN INTERLINGUA

Nostre presente criterios pro le diagnose de morbo de von Willebrand es summarisate in le paragraphos sequente, durante que exemplos illustrative seligite inter patientes recentemente studiate es presentate in Tabula 1.
A. Tempore prolongate de sanguination e nivellos subnormal de globulina antihemophilic (GAH):

Quando iste anormalitate, transmittitse como character autosomal dominante, es trovate in plure membros del familia, illo es considerate como diagnostic pro iste patientes e pro lor clinicamente afficite consanguieneos, mesmo si iste ultimes manifesta al tempore presente ambe defectos (Caso 10). In le absentia de studios familial, le diagnose etiam pote esser facite pro subjectos individual si le antecedentes de sanguination in consanguieneos es compatible con hereditage autosomal (Casos 3, 13, 18). Quando le studios familial es negative (i.e., quando il se tracta de casos sporadic) o quando information in re le antecedentes familial non es obtenibile, un diagnose de typic morbo de von Willebrand esseret etiam formulate (Casos 1, 2, 4, 14, 15, 16), excepte quando instrinsec defectos plachettal es trovate (vide infra) o quando transfusiones de plasma non produce un progressive augmento del activitat de GAH.

B. Prolongate tempore de sanguination e normal GAH:

Le diagnose es considerate como “probabile” in tal patientes si le sequente criterios es satisfacite:
1. Es trovate nulle evidentia de un “intrinsic” anormalitate plachettal, reflectite per normal valores in le aggregation de plachettas, per le disponibilite de PF-3, e per le liberation de diposphato adenosinic per tissu conjunctive e kaolina.
2. Le adhesivitate del plachettas, determinate per le modificate test de Salzman, es anormal e/o le tempore de sanguination del patiente es reducite per le transfusion de plasma in un dosage de 13 a 15 ml per kg de peso corporee.

C. Normal tempore de sanguination e reduce GAH (Caso 17):

Un diagnose de “probabile” morbo de von Willebrand esseret a facer si:
1. Un configuration inequivoc de autosomal hereditage dominante, a base de datos familial, exclude le possibilitate de hemophilia.
2. Le test de Salzman es anormal.
3. Le transfusion de plasma ab donatores con hemophilia e etiam ab donatores normal resulta in un progressive augmento del concentration plasmatic de GAH.

D. Normal tempore de sanguination e normal GAH:

Le diagnose es considerate como “possibile” si:
1. Nulle evidentia es trovate pro un anormalitate “intrinsic” de plachettas (vide B.1.)
2. Le test de Salzman es anormal.

Le supra-formulate criterios es tentative e, sin dubita, non satisfacera omne investigatores. Pro render le situation ancora plus confuse, certe patientes qui pare haber le syndroirie “clasric” pote etiam haber anomal factor plachettal 3 o non responde con un synthese de GAH post le transfusion de plasma. Si o non mesmo le syndrome “classic” representa un spectro de disordines remane a determinar.

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VON WILLEBRAND'S DISEASE


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