Acquired von Willebrand’s Syndrome in Systemic Lupus Erythematosus

By JOSEPH V. SIMONE, JO ANN CORNET AND CHARLES F. ABILDGAARD

THE HEREDITARY NATURE of von Willebrand’s disease is well established and, although clinical manifestations are highly variable, most patients develop their initial hemorrhagic symptoms during early childhood. Acquired forms of von Willebrand’s disease have not been reported. The purpose of this report is to describe the unique combination of apparently acquired findings of von Willebrand’s disease associated with lupus erythematosus. In the patient to be described, the findings of von Willebrand’s disease disappeared following corticosteroid therapy of his systemic lupus erythematosus.

CASE REPORT

The patient, E.B., had been in generally good health from his birth in October 1949, until the present illness. He had had measles, mumps, chickenpox, and scarlet fever without sequelae. He had undergone circumcision at age 2 and tonsillectomy and adenoidectomy at age 10 without excessive bleeding. In 1962, at the age of 12, he began to experience frequent epistaxis. However, the bleeding could be controlled and he did not require hospitalization or blood transfusion. In December 1962, bleeding from an abrasion of the hard palate required vigorous local therapy. In January 1963, he began to bruise more easily than he had at any time before. In March 1963, at the age of 13, a dental extraction was followed by persistent bleeding in spite of vigorous dental therapy. When the bleeding persisted for three days, he was admitted to a local hospital where whole blood transfusions were given and the dental socket was packed. The bleeding finally stopped on the tenth hospital day. Laboratory studies at that time revealed a normal clotting time, prothrombin time, platelet count, clot retraction, prothrombin consumption, and a markedly prolonged partial thromboplastin time. The white cell count ranged from 2,900 to 6,100 during hospitalization. He was then referred to the University of Illinois Research and Educational Hospitals for diagnostic studies.

In April, the boy was seen in the Pediatric Hematology Clinic where a diagnosis of von Willebrand’s disease was made on the basis of the above history, a prolonged bleeding time, an abnormal partial thromboplastin time, and a factor VIII level of 17 percent. Similar abnormalities were detected in July and November of 1963 (Table 1). In vivo
VON WILLEBRAND’S SYNDROME

platelet adhesiveness was below the lower limit of normal on all three occasions. Normal results were obtained for the following tests: prothrombin time, prothrombin consumption, clot retraction, clotting time, platelet count, fibrinogen, hemoglobin, white cell count, and differential.

The parents and six siblings were healthy and had no history of unusual bleeding or of autoimmune diseases. A maternal aunt had rheumatoid arthritis.

He did well clinically until December 7, 1963, when, at the age of 14, he was given his first smallpox vaccination. A week later, his left shoulder became painful and he was seen by his local physician who found enlarged, tender left axillary lymph nodes and a single primary “take” at the site of vaccination. He was readmitted to the local hospital on December 16, at which time he was found to have 4+ proteinuria, a white cell count of 1,600, and a normal blood pressure. On December 17, he began to have pain in the elbows and thighs without swelling, redness, or heat which persisted for the succeeding month. On December 18, a red, crusty, pruritic rash appeared on the forehead and subsequently spread to the ears and the hands. He was given cortisone ointment for the rash, but received no systemic therapy. He was again referred to the Research and Educational Hospitals and was admitted on January 16, 1964.

In the month preceding admission, the patient had experienced anorexia, fatigue, a 7 pound weight loss, persistent pain in the elbows and thighs, and progression of the rash. Physical examination revealed a 14 year old Caucasian boy of normal stature and body build who did not appear acutely ill. The blood pressure was 110/60, pulse 80/min., and oral temperature 99.6 F. An erythematous, crusty eruption involved the skin of the forehead, ears, bridge of the nose, and malar area of the face. A few nontender cervical nodes were palpable. A tender mass of matted nodes about 4 cm. in diameter was palpated in the left axilla. Small, purplish, macular lesions were seen on the fingers of both hands. The abdomen was slightly tender; the edges of both the liver and the spleen were palpated 2 cm. below the costal margins and were smooth, rounded, and tender. The examination was otherwise unremarkable.

The hemoglobin was 9.8 Gm./100 ml. The white cell count was 3,100 with 34 per cent segmented neutrophiles, 59 per cent lymphocytes, 5 per cent monocytes, 1 per cent eosinophiles, and 1 per cent basophiles. The platelet count was 108,000 per mm.3 The urine gave a 4+ test for protein, was grossly bloody, and contained many granular casts. Culture of the urine yielded no growth. Creatinine clearance was 4.5 ml./min. The blood urea nitrogen was 29 mg. and the serum creatinine 1.2 mg./100 ml. Chest x-ray, intravenous pyelogram, and electrocardiogram were normal.

Serum albumin was 3.1 Gm. and serum globulin 3.3 Gm./100 ml. The direct Coombs’, Kahn, latex fixation, and anti-streptolysin-0 tests were negative. The indirect Coombs’ test was positive, the Wasserman test gave a 4+ reaction, the erythrocyte sedimentation rate was 54 mm. per hour, serum antinuclear antibodies were present, and tests for lupus erythematosus cells were positive on three different days.

Coagulation studies again revealed abnormalities consistent with the diagnosis of von Willebrand’s disease (Table 1, January 1964). Circulating anticoagulants were not detected. His plasma was tested for circulating anticoagulants by mixing it with normal plasma in varying proportions (1:3, 1:1, 3:1) and performing a partial thromboplastin time on the mixture before and after incubation for one hour at 37 C. The partial thromboplastin time of the normal plasma was not prolonged by the patient’s plasma in any of the mixtures. As before, normal results were obtained for the clotting time, clot retraction, prothrombin time, prothrombin consumption, and platelet count.

The parents and six siblings had normal levels of factor VIII and normal bleeding times. Their sera were tested for antinuclear antibodies and none were found. A sample of the patient’s serum, collected in November 1963, two weeks before his vaccination, had been frozen and saved. That serum was positive for antinuclear antibodies.

On January 24, therapy was started with prednisone, 1.5 mg./Kg. body weight daily in divided doses. In the next few weeks, the hemoglobin fell to 6.5 Gm./100 ml., necessitating a transfusion of packed red cells. He began to feel better and the rash began to clear. How-
Table 1.—Serial Studies of Hemostatic Function

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Values†</th>
<th>April 63</th>
<th>July 63</th>
<th>Nov. 63</th>
<th>Jan. 64‡</th>
<th>May 64</th>
<th>June 64</th>
<th>Dec. 64-11 May 67</th>
<th>June 67</th>
<th>Oct. 67</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding time*</td>
<td>3-11 min.</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>7</td>
<td>7</td>
<td>3-7</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Partial thromboplastin time²</td>
<td>45-80 sec.</td>
<td>123</td>
<td>120</td>
<td>125</td>
<td>130</td>
<td>47</td>
<td>62</td>
<td>55-61</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Factor VIII³</td>
<td>50-200%</td>
<td>17</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>308</td>
<td>124</td>
<td>68-125</td>
<td>84</td>
<td>93</td>
</tr>
<tr>
<td>Platelet count</td>
<td>150,000-260,000</td>
<td>160,000</td>
<td>180,000</td>
<td>108,000</td>
<td>283,000</td>
<td>250,000</td>
<td>285,000</td>
<td>160,000-380,000</td>
<td>188,000</td>
<td>230,000</td>
</tr>
<tr>
<td>Platelet adhesiveness in vivo²</td>
<td>350,000/mm.²</td>
<td>24-58%</td>
<td>23</td>
<td>0</td>
<td>22</td>
<td>40</td>
<td>70</td>
<td>80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The bleeding time was performed by a modification of the Ivy technic similar to that suggested by Borchgrevink and Waaler.† Using a #15 surgical blade and a metal guide, two cuts, each 1.5 mm. deep and 10 mm. long, were made on the volar surface of the forearm. The normal range reported is that obtained using this method on 50 children and 50 adults.

†In authors’ laboratory.

‡The patient was vaccinated on December 7, 1963. Symptoms of systemic lupus erythematosus began a week later, and corticosteroid therapy was started on January 24, 1964.
ever, the hemoglobin again fell and was accompanied by a reticulocytosis of 4.0 percent. He became hypertensive, markedly Cushingoid, edematous, and he rapidly gained 35 pounds. After the dose of prednisone was lowered to 1 mg./Kg. daily and chlorothiazide was given twice weekly, the edema, hypertension, and excessive body weight improved. After two months of prednisone, the rash had cleared; after three months, the spleen could no longer be felt and the hemoglobin had risen to 10 Gm./100 ml.; in May 1964, after four months of prednisone, the patient volunteered that he no longer bruised or bled easily. At that time, the hemogram, bleeding time, and partial thromboplastin time had become normal and the factor VIII level had risen to 308 percent. But hematuria, proteinuria, hypertension, and serum antinuclear factor persisted. In June, prednisone was stopped and the patient was given methylprednisolone, 100 mg. in a single morning dose every forty-eight hours, which was equivalent to 2 mg./Kg. (120 mg.) of prednisone. Corticosteroid side effects lessened, but the urinary findings improved very slowly. The dose of methylprednisolone was gradually reduced over the next nine months to 16 mg. every forty-eight hours (equivalent to 20 mg. of prednisone) which was maintained until May 1967.

In November 1964, because hematologic and coagulation studies were consistently normal in the face of persistent proteinuria and microscopic hematuria, the patient was hospitalized for a renal biopsy; it was performed without incident. The biopsy interpretation by Dr. Conrad Pirani was as follows: “Proliferative glomerulonephritis consistent with early lupus nephritis—local and generalized proliferation in the axial and peripheral areas of the glomerulus consisting of both cells and matrix. The glomeruli show a tendency to lobulation. Basement membranes are not thickened; tubules, vessels and interstitial tissue are unremarkable.”

During 1965 and 1966, the patient continued to do well clinically. Hemograms and coagulation studies were repeatedly normal. He became normotensive in March 1965. LE-cell tests were repeatedly positive, but the number of LE-cells in each preparation gradually diminished. Normal levels of beta-1-C-globulin were found on three occasions in 1965. During 1966, urinary erythrocytes, casts, and protein returned to normal Addis values in that order.

In May 1967, corticosteroids were stopped after a total of forty months of therapy. In June and in October 1967, hematologic and coagulation studies were again normal and the patient remained asymptomatic. The LE-cell test was slightly positive in June and negative in October.

**Discussion**

Von Willebrand’s disease is typically a hemorrhagic disorder of variable severity, inherited as an autosomal dominant, primarily manifested by mucous membrane bleeding, and characterized by a prolonged bleeding time and a subnormal level of factor VIII. The bleeding disorder in the patient described above was typical in every way except for evidence that it was acquired rather than inherited. First, symptoms did not appear until he was 12 years old. He underwent circumcision, tonsillectomy, adenoidectomy, and open repair of a fractured humerus before that age without incident. Second, the family history was negative for unusual bleeding, and the bleeding times and factor VIII levels of the parents and six siblings were normal. And third, all clinical and laboratory manifestations of von Willebrand’s disease disappeared during corticosteroid therapy and failed to reappear after therapy was stopped. Therefore, instead of von Willebrand’s disease, a more correct diagnosis in this case would appear to be von Willebrand’s syndrome accompanying systemic lupus erythematosus.

Bleeding in systemic lupus erythematosus is most often a result of severe thrombocytopenia, a circulating anticoagulant, or corticosteroid therapy. In
the above case, the platelet count was at no time less than 108,000/mm³, and neither general nor specific tests indicated the presence of circulating anticoagulants. Further, clinical and laboratory manifestations of the bleeding disorder preceded corticosteroid therapy by two years. Hyperglobulinemic purpura has been reported in systemic lupus erythematosus,[7] but serum protein electrophoresis failed to disclose an abnormal component in this patient.

Acquired factor VIII deficiency with a normal bleeding time has been reported by Nilehn in patients with a variety of hematologic and hepatic diseases.[8] In twenty-two patients fibrinolytic activity was pathologically elevated, six patients had macroglobulinemia, and in three patients a circulating anticoagulant of factor VIII was found. Many of the remainder had associated coagulation abnormalities, such as deficiency of other coagulation factors, thrombocytopenia, or thrombocytosis. Three patients with factor VIII deficiency had unspecified “collagen disease,” but further clinical or laboratory details were not given. Platelet adhesion was not studied.

Coagulation studies in our laboratory in six additional children with systemic lupus erythematosus failed to disclose evidence of von Willebrand’s syndrome. However, three of these patients were on corticosteroid therapy at the time.

Corticosteroid therapy causes transient elevation of factor VIII levels in patients with rheumatic carditis, idiopathic thrombocytopenic purpura, and moderately severe or mild classical hemophilia.[9] Similar studies in five normal subjects and five patients with von Willebrand’s disease have revealed transient factor VIII elevation with no change in platelet adhesiveness.[10] Unpublished studies in our laboratory have confirmed the elevation of factor VIII in normals given corticosteroids, and in addition, no acute change was observed in the bleeding times of two patients with von Willebrand’s disease who received corticosteroids for one week. In the patient described above, corticosteroid therapy was followed by a return to normal of the bleeding time as well as the factor VIII level which was maintained after cessation of therapy. Therefore, these changes appear related to successful therapy of systemic lupus erythematosus rather than to a direct effect on factor VIII or hemostasis.

The intimate relationship, in this case, of von Willebrand’s syndrome and systemic lupus erythematosus was confirmed not only by the effect of corticosteroids, but also by the finding of antinuclear antibodies in a sample of the patient’s serum which had been collected before the clinical manifestation of systemic lupus erythematosus. The mechanism of this relationship is obscure. The coagulation abnormalities previously reported to accompany systemic lupus erythematosus were not found.[6] Although the prolonged bleeding time might be explained by undetected abnormal serum proteins interfering with normal platelet function in vivo,[11] or by an inflammatory effect on blood vessels,[12] the cause of the coexisting factor VIII deficiency is enigmatic in the absence of a circulating anticoagulant. It has been suggested that the “von Willebrand factor” controls both the bleeding time and factor VIII synthesis.[13] Since abnormal protein synthesis is known to be associated with systemic lupus erythematosus, it is possible that production of the von Willebrand factor was altered or that an antibody to the von Willebrand factor was produced.
In retrospect, cross transfusion studies would have been of interest and might have further characterized the nature of the von Willebrand-like defect in the patient. If the unusual nature of his acquired defect had been recognized prior to the treatment of systemic lupus, it would have been possible to study the effect of normal and/or hemophilic plasma transfusion on his bleeding time and factor VIII levels. In addition, an attempt to demonstrate an “antibody” to the von Willebrand factor might have been possible by transfusing a mixture of the patient’s plasma with normal or hemophilic plasma into a known von Willebrand’s disease recipient, in order to reveal possible inhibition of bleeding-time correction and the expected anomalous rise of factor VIII usually observed in such studies.

Summary

A boy is described with clinical and laboratory manifestations which were indistinguishable from von Willebrand’s disease. However, the relatively recent onset of symptoms, the negative family history, and the normal coagulation studies in both parents and six siblings led to the belief that the bleeding syndrome was acquired rather than inherited. The patient subsequently developed systemic lupus erythematosus following a smallpox vaccination. The findings of von Willebrand’s syndrome disappeared following corticosteroid therapy and did not return after cessation of therapy.

Acknowledgments

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References


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