A New von Willebrand Variant (Type I, New York): Increased Ristocetin-Induced Platelet Aggregation and Plasma von Willebrand Factor Containing the Full Range of Multimers

By Harvey J. Weiss and Ira I. Sussman

We report three members of a family who had reduced levels of plasma von Willebrand factor (vWF) and increased ristocetin-induced platelet aggregation (RIPA) (aggregation of platelet-rich plasma with ristocetin at a concentration of 0.45 mg/mL), as previously reported in type IIB and pseudo-von Willebrand's disease (vWD). However, in contrast to the latter two disorders in which the larger vWF multimers are absent in plasma, the entire range of vWF multimers was observed in the patients' plasma after sodium dodecyl sulfate–agarose gel electrophoresis, and all vWF multimers (including the largest) were present in the same proportion as in normal plasma and type I vWD. Thus, despite increased RIPA, the levels and multimeric pattern of vWF in this family's plasma were indistinguishable from those in type I vWD in which RIPA is usually decreased. Addition of ristocetin to the patients platelet-rich plasma resulted in the removal of vWF (and, more selectively, of the large multimers) at lower concentrations of ristocetin than normal, as in type IIB and pseudo-vWD. The defect in the patients was localized to their vWF, which had an enhanced capacity for aggregating washed normal platelets in the presence of low concentrations of ristocetin and for aggregating pseudo-vWD platelets (in the absence of ristocetin). Both glycoproteins (GP) Ib and Iib-IIIa were involved in the enhanced aggregation response. RIPA (at low ristocetin concentrations) in the patients' platelet-rich plasma was abolished by a monoclonal antibody (AP1) to GPIb and was markedly reduced by monoclonal antibodies (10E5 and LJP9) that block adenosine diphosphate and thrombin-induced binding of vWF and fibrinogen to GPIIb-IIIa but was unaffected by an antibody (LJP5) that only blocks vWF binding. Partial inhibition of the initial aggregation slope (and complete inhibition of second phase aggregation) was achieved with creatine phosphate/creatine phosphokinase. EDTA blocked second-phase aggregation but was without effect on the initial slope. The findings in this family combine some features of both type I vWD (normal pattern of vWF multimers in plasma) and type IIB vWD (increased RIPA) and further demonstrate the increasing complexity of the structure-function relationships in vWD.

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MATERIALS AND METHODS

Blood. Venous blood was mixed (9:1) with 3.2% sodium citrate and centrifuged to obtain platelet-rich plasma (PRP) and (platelet-poor) plasma as previously described.

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Bleeding time. The bleeding time was determined with a Simple-It bleeding time device (General Diagnostics, Morris Plains, NJ).

Standard hematologic studies on plasma. Prothrombin time and partial thromboplastin time (PTT) were determined by standard techniques, and specific coagulation factors (factors VIII and XI) were assayed with reference to pooled normal plasma by a one-stage technique\(^\text{11}\) using congenitally deficient plasmas as standard techniques, and specific coagulation factors (factors VIII and XI) were assayed with reference to pooled normal plasma by a one-stage technique\(^\text{11}\) using congenitally deficient plasmas as standards. Ristocetin cofactor in diluted plasma was assayed using washed normal platelets and a ristocetin concentration of 1.25 mg/mL.\(^\text{15}\)

Platelet studies. Platelets were counted by phase microscopy. Platelet aggregation induced in PRP by collagen, adenosine diphosphate (ADP), and epinephrine was studied in the aggregometer (Payton Associates, Buffalo) as previously described.\(^\text{15}\) Aggregation by graded concentrations of ristocetin was determined by adding 20 \(\muL\) of ristocetin (Lundbeck, Copenhagen) to 1.0 mL of PRP to achieve a final concentration ranging from 0.3 to 1.5 mg/mL. Results obtained were expressed as the initial slope of the aggregation curve (normalized to a chart speed of 20 mm/min) and as the maximal degree of aggregation.\(^\text{15}\) vWF antigen in platelets was measured on lysates of washed platelets by EIA as previously described.\(^\text{15}\) Platelet adhesion to rabbit subendothelium was measured by exposing deendothelialized segments of rabbit aorta to washed normal platelets and a ristocetin concentration of 1.25 mg/mL.\(^\text{15}\)

Special studies of vWF. Special studies on patient and normal vWF were performed using either plasma or various plasma fractions. Cryoprecipitate was prepared by thawing frozen (-70°C) citrated plasma (prepared as previously described) for 16 hours at 4°C.\(^\text{22}\) Further separation of vWF was obtained by agarose gel chromatography. Cryoprecipitate, 1.7 to 2 mL, was applied to a 2½ x 30-cm column of agarose A-15m, and elution was performed with 0.05 mol/L Tris-0.15 mol/L NaCl buffer, pH 7.1, as previously described.\(^\text{28}\) vWF multimers were identified by electrophoresis of plasma or platelet lysates in 0.1% sodium dodecyl sulfate (SDS)-1.5% glyoxyl agarose according to the method of Hoyer and Shainoff.\(^\text{7}\) Gels, 10 x 18 x 0.2 cm, were cast on gel bond film; 20-\(\muL\) of vWF (RAH vWF) was added to the agarose gel in the second phase of the electrophoresis. The sialic acid content of highly purified vWF was determined by Dr Sandor Shapiro (Jefferson College, Philadelphia), as previously described.\(^\text{30}\) From four to six units of plasma (1,000 to 1,500 mL) obtained by plasmapheresis, the latter kindly performed by Dr Randy Levine (St Luke's-Roosevelt Hospital Center). The ability of vWF in either plasma, cryoprecipitate, or vWF fractions to support aggregation of washed platelets was studied using platelets (from normal subjects) that had been separated from citrated PRP by albumin density gradient separation\(^\text{29}\) and suspended in calcium-free Tyrode's buffer (pH 7.3) at a final platelet count of 800,000 to 1,200,000/\(\muL\) as previously described.\(^\text{29}\) Adsorption of plasma vWF to platelets in the presence of ristocetin was performed as previously described.\(^\text{29}\) For these studies, a suspension of washed platelets was incubated with an equal volume of plasma in the presence of various concentrations of ristocetin for 30 minutes at 37°C, and after centrifugation at 2000 g for ten minutes, the supernatant plasmas were frozen at -70°C until studied. The vWF antigen in the supernatant was assayed by radioimmunoassay,\(^\text{31}\) (kindly performed by Dr Leon Hoyer, University of Connecticut Health Science Center, Farmington) and vWF multimers were determined as described previously.

Platelet inhibitors. The inhibitory effects of several monoclonal antibodies to platelet GP on RIPA was studied by the addition of these antibodies to PRP. A previously described\(^\text{32}\) monoclonal antibody (AP1) against platelet GPIb that blocks ristocetin-induced binding of vWF to platelets\(^\text{29}\) was kindly provided by Drs Robert Montgomery and Thomas Kunicki (Blood Center of Southeastern Wisconsin, Milwaukee). A monoclonal antibody (10E5) against GPIIb-IIIa was a gift from Dr Barry Collier (State University of New York, Stony Brook). This antibody has been previously shown to block the binding of fibrinogen to thrombin and ADP (but not ristocetin)-stimulated platelets\(^\text{33}\) and, more recently, has been shown to block the binding of vWF, fibrinogen, and thrombospondin as well.\(^\text{34}\) Several other monovalent Fab fragments of monoclonal antibodies against GPIIb-IIIa were a gift of Dr Zaverio Ruggeri (Scripps Clinic and Research Foundation, La Jolla, Calif). Antibody LJP9 inhibits the thrombin and ADP-induced binding to GPIIb-IIIa of both vWF and fibrinogen.\(^\text{35}\) Antibody LJP5 inhibits the binding of vWF but not fibrinogen,\(^\text{35}\) and antibody LJP10 binds to BPIIb-IIIa without inhibiting uptake of either vWF or fibrinogen (Dr Z. Ruggeri, personal communication). A possible role for ADP was studied using PRP prepared from blood anticoagulated (9:1) with 3.2% sodium citrate containing 90 mmol/L creatine phosphate and 60 U/mL creatine phosphokinase (CP/CPK) (Sigma Chemical Co, St Louis). The effect of adding Na\(_2\)EDTA was also studied. The studies using CP/CPK, EDTA, and monoclonal antibodies 10E5 and LJP9 were performed at concentrations of these substances that completely abolished platelet aggregation by 20 \(\mumol/L\) ADP.

Patients. Three members of a family with a mild bleeding history were studied. Patient 1, the propositus, is a 24-year-old male who reported a lifelong history of easy bruising. He bled excessively after a tonsillectomy at age 2½ and received plasma transfusions as treatment for a trauma-induced hematoma in his leg at age 13. However, he did not bleed excessively after a herniorrhaphy at age 1½ yrs. His twin sister (patient 2) also bruises easily, bled excessively after a tonsillectomy at age 2½, and at age 16 received blood transfusions for treatment of a large, painful hematoma on the buttocks. A second sister, aged 29, was not studied but is said to bruise easily and had life-threatening hemorrhage after a tonsillectomy at age 4. In addition, she suffered a hemarthrosis of the right ankle at age 23 (for which she received cryoprecipitate) and, in the same year, was treated with fresh-frozen plasma for about ten days after right knee surgery complicated by bleeding and the development of an anterior compartment syndrome. The 48-year-old mother of the propositus (patient 3) bled extensively after tooth extractions and postpartum, had one episode of unexplained gastrointestinal bleeding, and has received both plasma and cryoprecipitate for treatment of bleeding episodes. Patient 1 was studied by us on multiple occasions, and patient 2 was studied twice. Samples of frozen plasma on patient 3 (in whom variably depressed, but sometimes normal, levels of vWF and factor XI have been found.
RESULTS

Basic hematologic studies. Patients 1 and 2 were studied in our laboratory, and selected studies on patient 3 were done on samples of frozen plasma. Normal values were obtained for hemoglobin, white blood count, prothrombin time, and platelet count. Other studies are shown in Table 1. The bleeding time (performed once) was within the range of normal values. Factor VIII:C and vWF values on the propositus (patient 1) were obtained on four separate occasions. The average value obtained for Factor VIII:C was 26 U/dL; for vWF antigen, 38 U/dL; and for ristocetin cofactor, 41 U/dL. The relatively concordant decrease in these values is characteristic of the findings in type I vWD. The values of factor VIII:C, vWF antigen, and ristocetin cofactor obtained in his twin sister (patient 2) and mother (patient 3) were, in most cases, just at or somewhat below the lower limits of the control values (Table 1). The overall findings in the three affected family members studied suggest a diagnosis of type I-II vWD, and those with decreased plasma but normal platelet vWF levels (type I-2 vWD\textsuperscript{19}).

Multimeric structure of vWF. Figure 2 shows the multimer pattern of vWF in representative plasma samples for the three family members (patients 1, 2, and 3), three control subjects (N1, N2 [father of the propositus], N3), and three patients with typical type I vWD (two with type I-I and one with type I-2). The full range of vWF multimers was consistently present in all three patients; their multimer patterns were indistinguishable from those in control plasma or in patients with type I vWD. These patterns were observed in plasma samples obtained from patient 1 on four different days at intervals of 4, 2, and 2 months, from patient 2 on two samples obtained 1 week apart, and on one sample of plasma from patient 3. The conclusions drawn from visual examination of the gels were confirmed by densitometric scan in that the percentage of the total vWF contributed by the larger multimers (those of mol wt greater than band 6), as well as by all other multimers, were the same in the three affected family members as in the controls or type I subjects (Table 2). The pattern of vWF multimers in their platelets was also normal (data not shown).

Enhanced capacity of patient vWF to support ristocetin aggregation. Several types of studies were done that demonstrated that the enhanced RIPA in the affected family members was due to an abnormality in their plasma vWF. In one group of studies, platelet aggregation induced by increasing concentrations of ristocetin was assessed in a mixture containing washed normal platelets and either cryoprecipitate (at a final vWF antigen concentration of 35 U/dL) or

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<th>Table 1. Laboratory Studies</th>
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<tr>
<td>Bleeding time (min)</td>
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<tr>
<td>Plasma values (U/dL)</td>
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<tr>
<td>Factor VIII: C</td>
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<tr>
<td>vWF antigen (EIA)</td>
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<tr>
<td>Ristocetin cofactor</td>
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<tr>
<td>Factor XI</td>
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<tr>
<td>Platelets</td>
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<tr>
<td>Number ($\times 10^9$)/µL</td>
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<tr>
<td>vWF antigen (U/10^9)</td>
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<tr>
<td>Ristocetin aggregation‡</td>
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<tr>
<td>0.3 mg/mL</td>
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<td>0.45 mg/mL</td>
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<td>0.9 mg/mL</td>
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<td>1.2 mg/mL</td>
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*Assayed on frozen plasmas. (See Note Added in Proof).
†Performed elsewhere.
‡Control values obtained on eight to 13 normal subjects.

In patients 1 and 2, average results shown for plasma values and ristocetin aggregation are for studies obtained on four and two separate days, respectively.

RIPA. On all occasions studied, the addition of ristocetin to the PRP of both patients 1 (four occasions) and 2 (two occasions) resulted in platelet aggregation (60% to 91%) at concentrations (0.45 and 0.60 mg/mL) that never produced aggregation in normal subjects (Fig 1 and Table 1). This enhanced response to ristocetin is typical of previous findings in type IIB\textsuperscript{4,19,20} and pseudo-\textsuperscript{22} or platelet-type vWD\textsuperscript{23–25}. No aggregation resulted upon the addition of either cryoprecipitate or vWF fractions to patient PRP (data not shown), nor was spontaneous aggregation observed.
plasma (at a final vWF antigen concentration of 20 U/dL). The enhanced capacity of cryoprecipitate from patient 1 to support RIPA at low concentrations of ristocetin is shown in Fig 3A and 3B. Similar studies using plasma are shown in Fig 3C and demonstrate the enhanced capacity of vWF from patients 1, 2, and 3 to support RIPA when compared with plasmas from normal subjects or from patients with either type I-1 or type I-2 vWD. The experiment was modified by using, instead of a fixed concentration of vWF, increasing concentrations of vWF and a fixed, low concentration (0.6 mg/mL) of ristocetin. The enhanced capacity of vWF from patient 1 to support platelet aggregation by a low concentration of ristocetin is shown in Fig 3D. Finally, the increased reactivity of patient vWF with platelets in the absence of ristocetin was demonstrated using PRP from a subject with pseudo-vWD. We have previously shown that platelets from these patients are aggregated by human vWF without a requirement for ristocetin.22 The enhanced capacity of vWF from patients 1 and 2 to induce platelet aggregation in a patient with pseudo-vWF is shown in Fig 4.

Table 2. Densitometric Scan of vWF Multimers in Plasma

<table>
<thead>
<tr>
<th>Multimer No.</th>
<th>Normal</th>
<th>Patients</th>
<th>Type I vWD</th>
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<tr>
<td></td>
<td>N1</td>
<td>N2 N3</td>
<td>1 2 3 I-2</td>
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<tr>
<td>&gt;6</td>
<td>60</td>
<td>53 58</td>
<td>56 55 57</td>
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<tr>
<td>1</td>
<td>6</td>
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<td>7 7 9</td>
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*The percentage of the total vWF for bands 1 (the multimer of lowest mol wt) through band 6 and for the vWF accounting for all multimers with mol wt > band 6, determined by densitometric scan of the gels shown in Fig 2.

Increased adsorption to platelets of vWF and of the larger vWF multimers from patient plasma in the presence of ristocetin. In these studies, increasing concentrations of ristocetin were incubated at 37 °C for 30 minutes with a mixture containing equal volumes of washed normal platelets and plasma from either a normal subject or patient 1. The final vWF antigen concentration in the mixture without ristocetin was 20 U/dL, obtained in the case of the normal subject by prior dilution with plasma from a patient with severe (type III) vWD. After centrifugation, the vWF antigen content in the supernatant was measured by radioimmunoassay, and the percentage of vWF antigen remaining (not adsorbed to platelets) was calculated with reference to a control incubation mixture. In addition, the multimer pattern of vWF in each supernatant sample was determined. Figure 5 demonstrates the enhanced ristocetin-induced adsorption of vWF and the larger vWF multimers observed with the plasma of patient 1. In contrast to this abnormality of plasma vWF, the capacity of the patient's platelets to adsorb normal vWF with increasing ristocetin concentrations was the same as in normal platelets (data not shown).
Platelet adhesion to subendothelium. Platelet adhesion to subendothelium, studied in citrated blood at a shear rate of 2,600 s⁻¹, was normal in both patients 1 and 2 (58% and 55% control values of 42% ± 5%). To study specifically the properties of patient vWF in supporting adhesion, we added increasing concentrations of normal or patient vWF (in cryoprecipitate) to samples of citrated blood from a patient with severe (type III) vWD and then studied platelet adhesion to subendothelium. When compared at comparable levels of vWF antigen, the ability of patient vWF to correct the adhesion defect in type III vWD was, if anything, somewhat greater than that observed with normal vWF (data not shown).

DISCUSSION

Except for the enhanced platelet aggregation of their platelets by low concentrations of ristocetin, many of the findings in the family reported herein are those of type I vWD. Thus, factor VIII:C and vWF-related properties,
particularly in the propositus (patient 1), were decreased concordantly, and the complete range of vWF multimers was observed in their plasma (Fig 2). In addition, the proportion of the larger multimers to the total vWF was the same as in normal subjects and patients with typical type I vWD (Fig 2 and Table 2), thereby distinguishing this family from patients designated as type I B 19 in whom the larger multimers are present, but decreased in amounts relative to the other multimers. We have previously identified other subtypes of type I vWD according to the content of vWF antigen in both plasma and platelets.18 In the subtype designated I-1, the amount of vWF antigen in both plasma and platelets was decreased, whereas platelet vWF antigen was normal in type I-2. Findings entirely similar to these have recently been reported by Mannucci et al.37 The family described herein had normal levels of vWF antigen in their platelets (Table 1) and hence has type I-2 vWD according to our nomenclature. Neither we nor others have ever observed enhanced RIPA in type I vWD, and specifically, we did not observe this in two recently studied unrelated patients with the type I-2 subtype. Previously, an increase in RIPA has been described in only two disorders, type IIB vWD 4,5,19,20 and pseudo-type vWD, 22,23,24,38,39 in both of which the larger vWF multimers are absent in plasma. Since the family reported herein has a type I plasma vWF multimer pattern, they cannot be classified as having either of these two disorders. However, as in type IIB vWD, the defect was clearly localized to an abnormality in their vWF rather than in their platelets (as is the case in pseudo- or platelet-type vWD). Similar to the findings in type IIB vWD, 20 their vWF had a greater capacity for supporting platelet aggregation by low concentrations of ristocetin than vWF from normal subjects or from three patients with more typical type I vWD (Fig 3). In addition, patient vWF was more effective than normal vWF in aggregating the platelets of a patient with pseudo-vWD (Fig 4), demonstrating that the enhanced reactivity of their vWF towards platelets can be demonstrated in the absence of ristocetin. By analogy with type IIB, it might be appropriate to designate these patients as having type I B vWD, but since this term has already been used for another subtype of type I,36 we have chosen to designate our family as having vWD type I–New York or, alternatively, type IV vWD.

The basis for the enhanced capacity of the vWF in patients with vWD type I–New York to support platelet aggregation by low concentrations of ristocetin remains to be determined. As in type IIB vWD,19,20 this enhanced aggregation was associated with increased adsorption to platelets of vWF and, more specifically, of the larger vWF multimers (Fig 5), which may bind to GPIb with the highest affinity.31 Not surprisingly, platelet aggregation by low concentrations of ristocetin was completely blocked by a monoclonal antibody to GPIb since aggregation by ristocetin requires, initially, the binding of vWF to this platelet membrane GP 10-13.35 Aggregation by low concentrations of ristocetin was also greatly diminished by monoclonal antibodies to GPIb-IIIa (10E5 and LPJ9) that block ADP- and thrombin-induced binding of vWF and fibrinogen to this membrane GP,33,35 but was not inhibited by antibody LPJ5, which only blocks vWF binding.35 These findings together with the inhibitory effect of the ADP-consuming system CP/CPK suggest that the binding to GPIb-IIIa of fibrinogen (but not vWF) through endogenous platelet ADP may also contribute to the enhanced RIPA in vWD type I–New York. These conclusions are consistent with recent studies that have demonstrated that the binding of fibrinogen to GPIb-IIIa plays a role in the aggregation of normal platelets that is initiated by binding of vWF to GPIb.40,42 The enhanced initial response to low concentrations of ristocetin in the presence of EDTA (which blocks binding of proteins to GPIb-IIIa)40 may be related to the fact that calcium is not required for the initial binding of vWF to GPIb 41 and suggests that this binding may even be enhanced in vWD type I–New York.

Several aspects of this disorder remain to be clarified. For one, it is not clear why, as in type IIB vWD, the larger multimers are more selectively removed from plasma by low concentrations of ristocetin, yet (unlike type IIB) the native plasma contains the full range of multimers (and the same proportion of larger multimers as in normal plasma). In theory, an increased clearance of larger multimers from plasma, as in type IIB vWD,20 could be compensated for by increased synthesis, but we have no evidence to support this possibility. The relationship of the abnormal vWF in vWD type I–New York to the bleeding disorder in this family is also not entirely clear. Platelet adhesion (in citrated blood) to subendothelium was not diminished in these patients under conditions that have demonstrated decreased adhesion in patients with severe vWD,20 although we have not systematically studied patients with milder forms of type I vWD. However, we found no evidence to suggest that the vWF in type I–New York is deficient in its capacity to support platelet adhesion, and in fact, where this was specifically examined, vWF type I–New York appeared to correct the
platelet adhesion defect in severe vWD to a greater extent than normal vWF. An interpretation of the findings in this study is further complicated by the somewhat decreased factor XI values in two members of the family, although this was normal in one other clinically affected family member (patient 2) and was said to be normal in a second severely affected sister of the propositus who was not studied by us. In all likelihood, the bleeding disorder in the family is probably the result of low to marginal levels of vWF and factor VIII:C, and in some cases, factor XI, which are unable to support normal hemostasis under some circumstances. The findings in the present study demonstrate further the evolving complexity of the clinical and laboratory findings in vWD and demonstrate the problems in involved in attempting to define the disorder in terms of either the plasma multimer patterns or functional studies such as those involving ristocetin aggregation. The family designated as having vWD type I—New York in the present study has features of both type I vWD (multimer patterns) and type IIB vWD (enhanced ristocetin aggregation) and underscores the desirability of assigning, ultimately, subtypes on the basis of the molecular defects in the vWF protein.

NOTE ADDED IN PROOF

We recently studied patient 3 in our laboratory and, on freshly drawn blood specimens, obtained values as follows: platelet aggregation 61% at a ristocetin concentration of 0.6 mg/mL. Factor VIII: C = 64 U/dL, Factor XI = 65 U/dL, vWF antigen = 52 U/dL, and ristocetin cofactor = 50 U/dL. Platelets, 305,000/μL; bleeding time, 7 min.

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A new von Willebrand variant (type I, New York): increased ristocetin-induced platelet aggregation and plasma von Willebrand factor containing the full range of multimers

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