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Upshaw-Schulman Syndrome Revisited: A Concept of Congenital Thrombotic Thrombocytopenic Purpura

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Abstract

Upshaw-Schulman syndrome (USS) is a congenital bleeding disorder characterized by repeated episodes of thrombocytopenia and microangiopathic hemolytic anemia that respond to infusions of fresh frozen plasma. Inheritance of USS has been thought to be autosomal recessive, because 2 siblings in the same family are often affected but their parents are asymptomatic. Recently, chronic relapsing thrombotic thrombocytopenic purpura (CR-TTP), reported almost exclusively in adults, was shown to be caused by inherited or acquired deficiency in the activity of a plasma von Willebrand factor–cleaving protease (vWF-CPase). The pathogenesis of USS is unknown, and a relationship between CR-TTP and USS has not been reported. We studied 3 unrelated USS patients (ST, SY, and KI) who presented with severe indirect neonatal hyperbilirubimenia. All 3 patients had undetectable vWF-CPase activity, and the inhibitors to vWF-CPase were all negative. In their parents with no clinical symptoms, vWF-CPase activities as a percentage of control samples (mother/father) were 17/20 for ST, 60/45 for SY, and 36/5.6 for KI. Thus, USS and vWF-CPase activity appear to be coinherited as autosomal recessive traits. Transfusion of fresh frozen plasma in 2 patients (ST and SY) resulted in the expected maximal increment of approximately 7% to 8% in vWF-CPase activity at 1 to 4 hours, but the levels became less than 3% within 2 days. After this decrease, platelet counts increased, plateaued in the normal range at 10 to 12 days, and declined thereafter. Thus, the 2 to 3 weeks of therapeutic benefit from plasma infusions will be discussed in relation to the intravascular lifetime of vWF-CPase. *Int J Hematol.* 2001;74:101-108.

Key words: Upshaw-Schulman syndrome; Chronic relapsing TTP; von Willebrand factor–cleaving protease; Fresh frozen plasma

1. Introduction

In 1960, Schulman et al [1] described an 8-year-old girl born in Germany who had repeated episodes of bleeding associated with chronic thrombocytopenia and microangiopathic hemolytic anemia (MAHA), but without specific clotting factor abnormalities. The onset of her bleeding episodes could be traced back to the neonatal period, when she had a large ecchymosis on the dorsum of one hand. Interestingly, the abnormal bleeding, thrombocytopenia, and MAHA were transiently but dramatically corrected by the infusion of normal fresh frozen plasma (FFP). Therefore, the authors proposed that the patient might have a congenital deficiency of a plasma platelet-stimulating factor. In 1978, Upshaw [2] described a 29-year-old woman who, from the age of 6 months to 12 years, had 6 to 10 episodes per year characterized by thrombocytopenia and MAHA, similar to Schulman's case. Rennard and Abe [3] described a case similar to Upshaw's with a slightly decreased level of plasma cold-insoluble globulin (fibronectin) during the acute phase but normal levels between episodes. Furthermore, they proposed the nomenclature of Upshaw-Schulman syndrome (USS) for such patients. The correlation of fibronectin level and disease activity, however, could not be confirmed in 2 USS patients, including Schulman's original case, by either Koizumi et al

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[4] or Goodnough et al [5], who found normal levels of plasma fibronectin regardless of clinical course. The inheritance of USS has been thought to be autosomal recessive, because 2 siblings in the same family are often affected but their parents are apparently asymptomatic. Based on these background studies, Moake et al [6] used the term chronic relapsing thrombotic thrombocytopenic purpura (CR-TTP) to describe the condition they observed in 4 TTP patients who showed a chronic relapsing clinical course, including both the Schulman case and the patients with an apparently acquired form. Importantly, Moake et al [6] demonstrated unusually large von Willebrand factor (vWF) multimers (UL-vWFMs) in their patients' plasma during the early remission stage. The clinical effectiveness of the infusion of factor VIII/vWF concentrate into a USS patient has been reported by Miura et al [7], and, conversely, the clinical exacerbation by the administration of DDAVP (1-desamino-8-D-arginine vasopressin) to USS patients has also been reported by Hara et al [8]. After thrombopoietin was cloned and sensitive assays were developed, a normal level of plasma thrombopoietin in 5 Japanese patients with USS was reported by Miura et al [9]. Thus, the pathophysiology of USS has remained unexplained, and evidence for a relationship between USS and CR-TTP has become obscure. However, a major advance in understanding CR-TTP followed the development of a quantitative assay for vWF–cleaving protease (vWF-CPase) activity, which specifically splits the tyrosine 842–methionine 843 bond of the vWF subunit in the presence of 1 to 1.5 mol/L of a mild protein denaturant such as urea or guanidine-HCl [10,11]. Furlan et al [12], after analyzing 4 patients belonging to 3 separate families, reported that CR-TTP was associated with deficiency of vWF-CPase activity.

In the present study, we have determined the plasma vWF-CPase activity in 3 Japanese patients with a clinical diagnosis of USS and in their family members. All 3 patients consistently showed a deficient state of plasma vWF-CPase activity when it was tested with plasmas obtained approximately 2 weeks after FFP infusion. The most striking clinical symptom of these 3 patients was severe hyperbilirubinemia, which developed soon after birth and required exchange blood transfusions. Thus, we re-evaluated USS to show that it is a congenital deficiency of vWF-CPase and that the parents are asymptomatic carriers. Furthermore, a unique transfusion effect of FFP on vWF-CPase activity in USS patients is shown.

2. Materials and Methods

2.1. Samples

Blood was collected in plastic tubes with a 1/10 volume of 3.8% Na_3-citrate as an anticoagulant. Citrated platelet-poor plasma was prepared by centrifugation at 3000*g* at 4°C for 15 minutes and stored in aliquots at –80°C until use. Human vWF was purified from cryoprecipitate as previously described [13].

2.2. Assays of vWF Parameters

A quantitative assay of vWF antigen (vWF:Ag) or ristocetin cofactor (vWF:RCo) was performed as previously described [14], using patient plasmas obtained 2 weeks after FFP infusion (see the "Patients and Results" section).

Sodium dodecyl sulfate (SDS)-1.4% agarose gel electrophoresis was performed according to the method of Ruggeri and Zimmerman [15]. After electrophoresis, Western blotting onto nitrocellulose membrane followed by luminographic detection of vWF-multimers (vWFMs) were performed according to the method of Budde et al [16] using Kodak XRP-1 film (Eastman Kodak, Rochester, NY, USA) and a Renaissance kit (NEN Life Science, Boston, MA, USA).

2.3. Assay of vWF-CPase

vWF-CPase activity in plasma was assayed according to the method of Furlan et al. [12], with a slight modification. Briefly, pooled normal human plasma (NHP) was serially diluted with 0.05 mol/L Tris-HCl (pH 7.4) containing 0.15 mol/L NaCl (TBS), and 10 μL of each dilution was mixed with 1 μL of 100 mmol/L phenylmethylsulfonyl fluoride (PMSF) (Wako Chemicals, Tokyo, Japan) dissolved in 99.8% methanol in Eppendorf tubes. Then, 90 μL of purified vWF (20 μg/mL) dissolved in urea buffer (1.5 mol/L urea per 0.05% NaN_3 per 10 mM $BaCl_2$ per 5 mmol/L Tris-HCl) (pH 8.0) was added to each mixture, and the tubes were capped and incubated at 37°C for 24 hours. After incubation, 10 μL of 100 mmol/L EDTA (pH 8.0) was added to each mixture to quench the enzyme activity. Under these conditions, a specific cleavage of the tyrosine 842–methionine 843 bond of the vWF subunit was identified by analyzing the amino acid sequence of the generated fragments as previously described [17]. A portion of each reaction mixture was separated by SDS–1.4% agarose gel electrophoresis, and the vWFMs were visualized by Western blotting and luminography, as described above. Quantitation of vWF-CPase was performed using scanning densitometry, as described by Furlan et al [18]. An activity value of 100% was defined as the amount of the enzyme contained in 1 mL of pooled NHP. The detection limit of vWF-CPase activity in this assay was approximately 3%, and the results obtained for normal subjects (n = 30; 12 female and 18 male, 23-47 years old) were 96.2 ± 37.4%.

2.4. Assays of vWF-CPase Inhibitor

The inhibitor activity against vWF-CPase was measured according to studies by Furlan et al [19] and Tsai and Lian [20] based on the Bethesda method, which was originally developed for the measurement of factor-VIII inhibitor [21]. Briefly, a test sample was first heat-inactivated at 56°C for 30 minutes. Then the sample was centrifuged at 15,000*g* at 4°C for 15 minutes, and the supernatant was saved. The supernatant or TBS (control) was mixed with pooled NHP in equal amounts and then further incubated at 37°C for 2 hours. After incubation, residual vWF-CPase activity was measured as described above. One unit of inhibitor was defined as the amount that reduced the vWF-CPase activity to 50% of the control. An inhibitor titer was also assayed using patient immunoglobulin (Ig) Gs that were purified from plasmas using a protein A sepharose CL-6B column (Pharmacia Biotech AB, Uppsala, Sweden), according to the manufacturer's instructions.

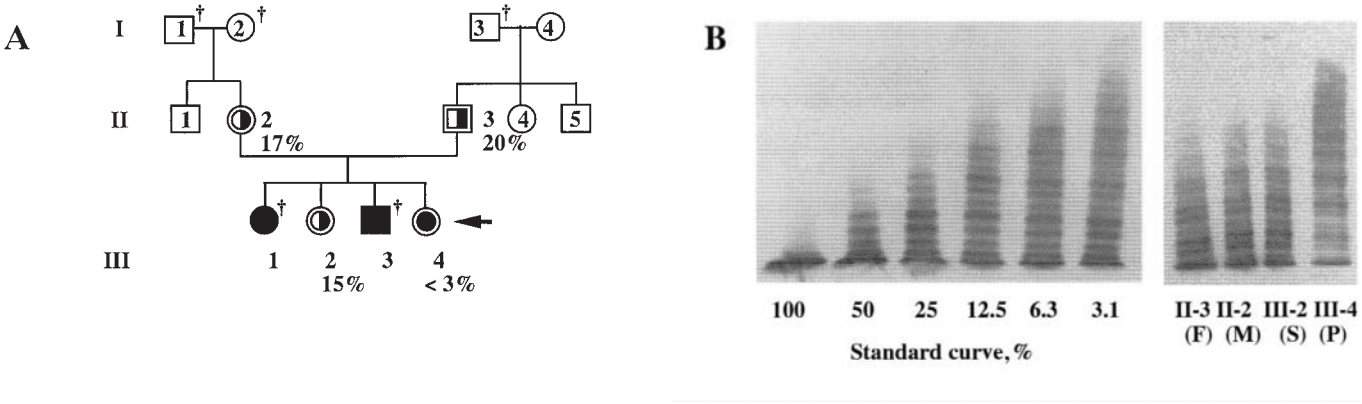

Figure 1. Patient ST family pedigree and von Willebrand factor–cleaving protease (vWF-CPase) activity. A, Circles are female and squares are male. Double circles and squares indicate that vWF-CPase activities were assayed, and single circles and squares were not assayed. Closed circles and closed squares represent bleeders, and the half-closed circles and squares represent asymptomatic carriers. The arrow indicates the proposita; † indicates deceased. B, Left panel is a standard curve in which percentages of vWF-CPase activity are shown. Right panel is the enzyme activity of case ST and her family members. F indicates father; M, mother; S, elder sister; and P, patient. Details of this assay and the results are described in "Materials and Methods" and in "Patients and Results."

3. Patients and Results

3.1. ST Family

The proposita (ST) was a Japanese girl born in Osaka in 1986, the fourth child of nonconsanguineous parents (Figure 1A). Soon after birth, the patient developed severe indirect hyperbilirubinemia (18.6 mg/dL) and thrombocytopenia (30,000/μL) of unknown etiology. Rho(D) and ABO blood groups were compatible between the neonate and the mother. The patient received exchange blood transfusion twice on the first day of life. The proposita's eldest sister died of melena on the fourth day after birth. Her elder brother died of spontaneous intracranial bleeding at the age of 13 years. He had an episode of severe jaundice in his neonatal period that required an exchange blood transfusion. Furthermore, he had clinical signs of repeated MAHA and chronic thombocytopenia very similar to those of the proposita. The proposita's parents and surviving elder sister had no sign of bleeding tendency. From birth to 4 years of age, the proposita had numerous episodes of hemolysis that were treated by plasma exchange or FFP infusion. A diagnosis of USS was made when she was 4 years old, based on the clinical findings of early-onset and repeated MAHA without specific coagulation abnormalities. From that time, she has received FFP infusions (5 mL/kg) every 2 to 3 weeks. At age 11, she developed thrombotic occlusion of the left internal carotid artery that resulted in right hemiparesis. Subsequently, she developed hypertension and proteinuria. The effect of FFP on her platelet count during 1998 is shown in Figure 2A. A similar increase to a normal platelet count was observed 7 to 10 days after each FFP infusion. The plasma level of vWF:RCo and vWF:Ag in the proposita were 190% and 120%, respectively, and UL-vWFM was also detected. UL-vWFMs were not detected in the plasmas of the patient's parents.

The assay of plasma vWF-CPase activity in this family is shown in Figure 1B. The activity of the proposita was below 3% of the control, and that of her father, mother, and sister showed moderately decreased levels of 20%, 17%, and 15%, respectively. Plasma vWF-CPase activity in the proposita was consistently less than 3% of the control on 11 different occasions between 1992 and 2000 at approximately 14 days after FFP infusion, using frozen plasmas stored at –80°C. The inhibitor titer to vWF-CPase in this patient and her parents was consistently less than 0.1 Bethesda units/mL, and the purified patient IgG (2.3 mg/mL, final) showed no inhibition of the enzyme activity. These findings were also confirmed by the consistent rise of platelet count after FFP infusion, as shown in Figure 2A and B. Furthermore, coinheritance of vWF-CPase activity and autosomal recessive trait of USS were also indicated.

Plasmas from the eldest sister and elder brother, both deceased, were not available, and their vWF-CPase levels are not known. However, a high similarity of the clinical course between the proposita and her elder brother strongly suggests that the latter had USS.

Subsequently, the effect of transfusion on vWF-CPase level was analyzed by the infusion of 2 units (approximately 160 mL) of FFP into the proposita (33 kg body wt). Changes in laboratory findings in peripheral blood after FFP infusion are described in Table 1. As shown in Figure 2B, the maximum increase of vWF-CPase activity was observed 4 hours after FFP infusion. That value, 8% of the control, was comparable with the expected value of approximately 10%. Within 2 days, enzyme activity was no longer detected (<3%) in the patient plasma, but, most interestingly, the platelet count began to rise after this, plateaued on days 7 to 11, and then decreased.

3.2. SY-Family

The proposita (SY) was a Japanese girl born in Sapporo in 1986, the first child of nonconsanguineous parents (Figure 3A). Fourteen hours after birth, the patient developed severe indirect hyperbilirubinemia (21.6 mg/dL) and thrombocytopenia (40,000/μL) of unknown etiology. She

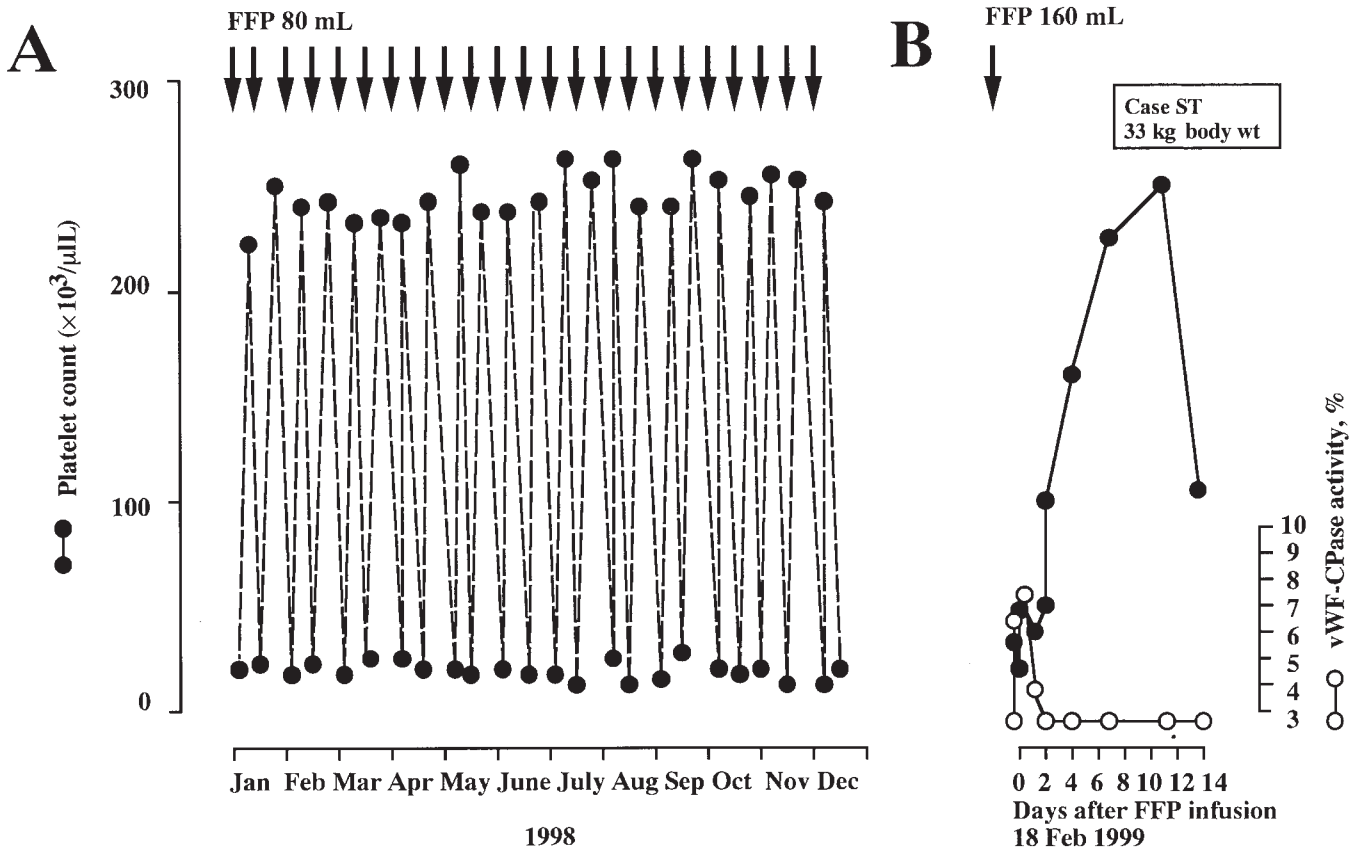

Figure 2. Fresh frozen plasma (FFP) infusions administered to patient ST. A, FFP (1 unit = 80 mL) was infused to an Upshaw-Schulman patient (patient ST, 32 kg body wt) every 2 weeks in 1998. On each occasion, a similar increase to a normal platelet count was observed 7 to 10 days after FFP infusion. B, FFP (2 units = 160 mL) was administered by infusion to patient ST (33 kg body wt), and the platelet count and von Willebrand factor–cleaving protease (vWF-CPase) assays were monitored. The peak of vWF-CPase activity was detected after 1 to 4 hours of FFP infusion, but within 2 days its activity was almost undetectable. The platelet count began to rise thereafter and plateaued 7 to 11 days after infusion, and then decreased again (see "Patients and Results").

received an exchange blood transfusion twice on the first day of life, and this treatment immediately corrected all the abnormalities. Both direct and indirect Coombs test results were negative. Her parents were apparently healthy and had no bleeding tendency. At 2 months of age, she again developed hemolysis and thrombocytopenia. Infusion of FFP dramatically improved her clinical signs, and a diagnosis of USS was made based on the early onset of repeated MAHA. From that time, she experienced frequent episodes of hemolytic crisis and thrombocytopenia. Thus, prophylactic

Table 1.
Changes in Laboratory Findings in Peripheral Blood After Fresh Frozen Plasma Infusion in Patient ST*

	Day 0†	Day 1	Day 2	Day 4	Day 7	Day 11	Day 14
White blood cell count, /μL	5270	4710	5710	6380	5030	5180	10,980
Red blood cell count, 10^4/μL	418	407	439	458	457	450	457
Hemoglobin, g/dL	11.3	10.9	11.8	12.5	12.4	12.2	12.3
Reticulocytes, %	1.9	ND	ND	ND	ND	ND	0.9
Total bilirubin, mg/dL	0.5	0.4	0.3	0.2	0.2	0.3	0.6
Glutamic oxaloacetic transaminase, IU/L	24	17	19	21	18	17	19
Glutamic pyruvic transaminase, IU/L	16	15	18	17	15	14	15
Lactate dehydrogenase, IU/L	687	505	530	506	425	397	480
Blood urea nitrogen, mg/dL	35.1	30.9	28.4	31.0	32.3	24.7	30.8
Creatinine, mg/dL	1.5	1.4	1.3	1.2	1.5	1.2	1.3

*ND indicates not determined.
†February 18, 1999.

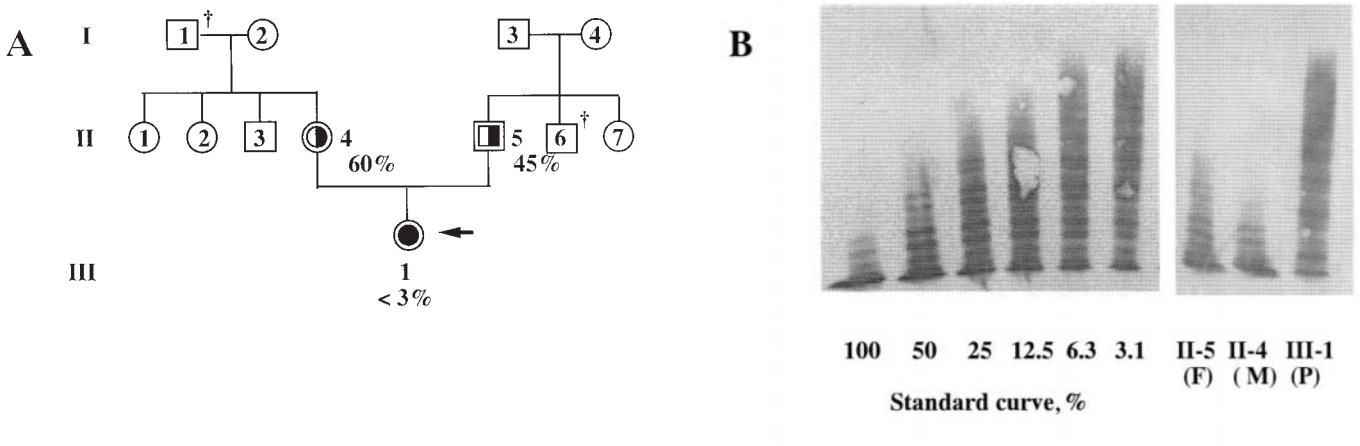

Figure 3. Patient SY family pedigree and von Willebrand factor–cleaving protease (vWF-CPase) activity. A, See Figure 1 for explanation of symbols and marks. B, Left panel is a standard curve in which percentages of vWF-CPase activity are shown. Right panel is the enzyme activity of case SY and her family members. F indicates father; M, mother; P, patient (see "Patients and Results").

infusion of FFP (5-10 mL/kg) every 2 to 3 weeks was started at age 11 months. During the acute phase of hemolysis, UL-vWFM was detected in her plasma as previously described [22] but was not detected in the plasmas of her parents. This patient now has transfusion-associated hepatitis C.

Assay of plasma vWF-CPase activity in this family is shown in Figure 3B. The enzyme activity of proposita was less than 3% of the control, and that of her father and mother was 45% and 60% of the control, respectively. The inhibitor titer to vWF-CPase in the proposita and her parents was uniformly less than 0.1 Bethesda units/mL, and the purified patient IgG (3.2 mg/mL, final) showed no inhibition on vWF-CPase activity. Thus, the mode of inheritance of USS and vWF-CPase deficiency appears to be autosomal recessive in this family. The plasma levels of vWF:RCo and vWF:Ag in the proposita were 220% and 190%, respectively, and UL-vWFM was also positive in plasma.

During the past few years, 3 units (approximately 240 mL) of FFP was administered to the proposita (40-45 kg body wt) by infusion every 14 to 18 days (Figure 4A). On 2 occasions, the effect of transfusion on vWF-CPase was analyzed (Figure 4A and B). The maximum increase in vWF-CPase activity to 8% to 10% was observed at 1 to 4 hours after FFP infusion, and that value was comparable with the expected value (approximately 10%). After 2 days, the protease activity was no longer detected. A rise in the platelet count began thereafter, plateaued at 7 to 10 days, and then decreased (Figure 4B), a similar pattern as that shown by patient ST. Changes in laboratory findings in the peripheral blood after FFP infusion in this patient are shown in Table 2.

3.3. KI-Family

The propositus (KI) was a Japanese boy and the second child of nonconsanguineous parents (Figure 5A). He was born in Osaka in 1999 by Caesarian section, with a gestational age of 37 weeks and 1 day and a birth weight of 2303 g. Ten hours after birth, the patient developed severe indirect hyperbilirubinemia (15.3 mg/dL) and thrombocytopenia (8000/μL). Because Rho(D) and ABO blood groups were compatible between the neonate and the mother and both the direct and indirect Coombs test results were negative, the etiology of severe jaundice was unknown. An exchange blood transfusion was performed, and the patient's hyperbilirubinemia resolved. Soon after this treatment, his platelet count returned to normal. He was discharged at age 20 days but soon had recurrent thrombocytopenia and MAHA, and a second exchange blood transfusion was performed at age 33 days. His parents were apparently healthy and had no bleeding tendency. A diagnosis of USS was made at the age of 3.5 months based on his clinical signs, and then he was treated with prophylactic infusion of FFP (5 mL/kg body wt) every 2 to 3 weeks.

The assay of plasma vWF-CPase activity in this family is shown in Figure 5B. The enzyme activity of the propositus was less than 3% of the control, and those of his father, mother, and elder sister were 5.6%, 36%, and 30% of the control, respectively. Of particular interest in this family is the father, 31 years old at the time of the study (born in 1969), who had an extremely low level (5% to 7% of the control) of vWF-CPase activity, which was tested on 3 separate occasions. Despite his extremely low activity of vWF-CPase, he was asymptomatic. Inhibitor to vWF-CPase was not detected in the propositus or his parents. The inheritance mode of USS and total vWF-CPase deficiency in this family is apparently autosomal recessive, with the proviso that the father had detectable but very low vWF-CPase activity. The plasma levels of vWF:RCo and vWF:Ag in the propositus were 160% and 130%, respectively. UL-vWF was also positive in the patient plasma but was negative in the plasmas of his parents.

4. Discussion

Of the patients with clinical diagnoses of CR-TTP, those with an early-onset type should be carefully evaluated, because the etiology of their TTP might be quite different from that of the late-onset type, which apparently often

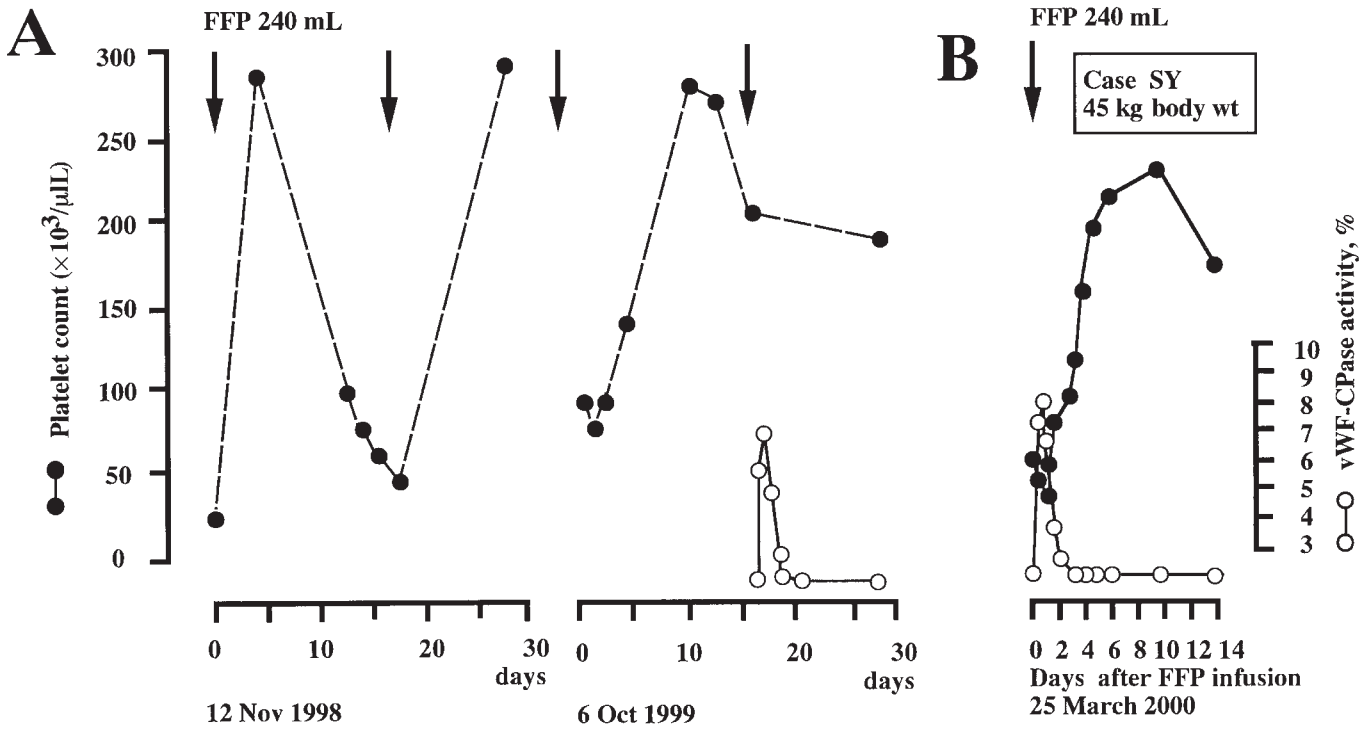

Figure 4. Fresh frozen plasma (FFP) infusions administered to patient SY. A, FFP (3 units = 240 mL) was administered by infusion to patient SY (38-45 kg body wt), and platelet count was determined. An increase to a normal platelet count was observed every 5 to 10 days after FFP infusion, except for 1 occasion. B, FFP (240 mL) was administered by infusion to patient SY (45 kg body wt), and platelet count and von Willebrand factor–cleaving protease (vWF-CPase) assays were simultaneously monitored. The vWF-CPase activity was detected after 1 to 6 hours of FFP infusion, but after 2 days it was almost undetectable. The platelet count began to rise after this, plateaued at 6 to 12 days, and then decreased again, a pattern closely resembling that observed in patient ST (Figure 2) (see "Patients and Results").

includes acquired TTP [23]. Here, we have presented 3 unrelated patients with early-onset TTP, who also uniformly had severe indirect hyperbilirubinemia, thrombocytopenia, and MAHA observed soon after birth, despite compatible feto-maternal Rho (D) and ABO blood groups and negative Coombs test results. For these patients with complex clinical signs, an exchange blood transfusion was lifesaving. Also, they quickly developed recurrent episodes of thrombocytopenia and MAHA that could be treated and then prevented by infusion of FFP every 2 to 3 weeks. For patients with such laboratory and clinical findings, a diagnosis of USS has been made [3]. Pediatric hematologists are more likely than general physicians to see patients with this diagnosis, and the essentially congenital symptoms that characterize USS may be overlooked. In fact, Furlan et al [12] described a breakthrough 1997 study of 4 patients with CR-TTP belonging to 3 families. Of the 4 patients, 2 (patients A1 and A2) were siblings with the early-onset disease, and both had an extremely low level of vWF-CPase activity that was determined on 2 different occasions. The other 2 patients (B and

Table 2.
Changes in Laboratory Findings in Peripheral Blood After Fresh Frozen Plasma Infusion in Patient SY*

	Day 0†	Day 1	Day 2	Day 5	Day 6	Day 10
White blood cell count, /μL	7000	5700	5200	4900	4700	5100
Red blood cell count, 10^4/μL	402	391	364	359	391	406
Hemoglobin, g/dL	12.4	12.2	11.4	12.3	12.1	12.6
Reticulocytes, %	1.0	1.8	1.3	2.0	1.1	ND
Total bilirubin, mg/dL	2.4	0.9	ND	0.5	0.8	0.8
Glutamic oxaloacetic transaminase, IU/L	34	37	ND	29	27	40
Glutamic pyruvic transaminase, IU/L	49	52	ND	46	40	53
Lactate dehydrogenase, IU/L	524	603	ND	344	327	535
Blood urea nitrogen, mg/dL	15.6	ND	ND	ND	17.2	15.3
Creatinine, mg/dL	0.5	ND	ND	ND	0.6	0.5

*ND indicates not determined.
†March 25, 2000.

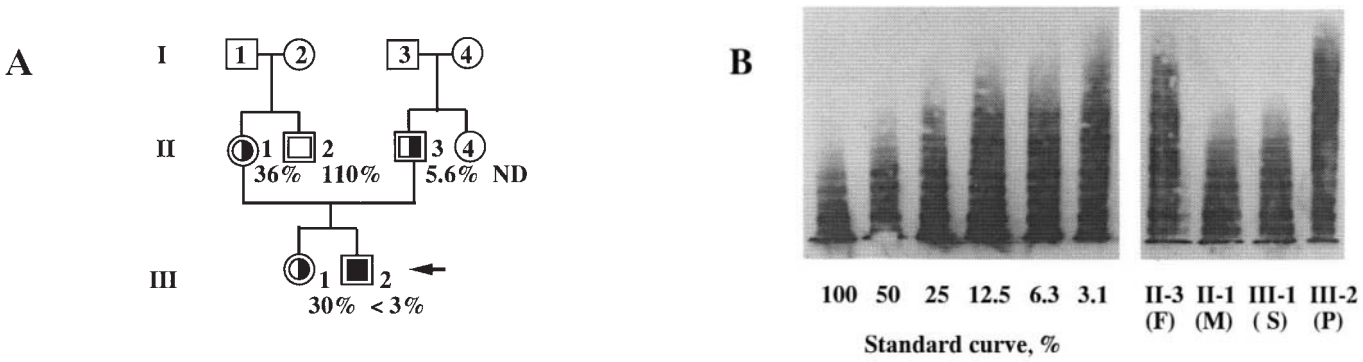

Figure 5. Family pedigree and von Willebrand factor–cleaving protease (vWF-CPase) activity in the family of patient KI. A, See Figure 1 for explanation of symbols and marks. A sibling of the father (II-4) had congenital heart failure (ventricular septum defect: VSD) and received a surgical operation without bleeding complications in his early childhood. B, Left panel is a standard curve in which the percentage of vWF-CPase activity is shown. Right panel is the enzyme activity of patient KI and his family members. F indicates father; M, mother; S elder sister; P, patient (see "Patients and Results").

C) were unrelated and the diseases of both were of the late-onset type. Both latter patients showed a deficient state of vWF-CPase activity on one occasion, but only a moderately decreased level on another occasion. This finding may simply suggest that the former differed from the latter in etiology for CR-TTP.

In addition to early onset of TTP, the 3 unrelated USS patients in the present study had a persistent deficiency of plasma vWF-CPase activity. In this regard, the present cases are similar to Furlan's cases A1 and A2 [12]. In the ST family, the deceased elder brother was assumed to be affected based on the similarity of clinical signs to the proposita. Furthermore, a significant decrease in vWF-CPase activity in the plasmas from both parents indicated that the disease inheritance in this family was autosomal recessive. The SY family also showed findings similar to the ST family. However, in the KI family, most interestingly, the father showed an extremely low level (5% to 7%) of vWF-CPase activity, but without clinical manifestations of MAHA and thrombocytopenia. This finding may simply suggest that his amount of vWF-CPase activity (>5%) is minimally required to prevent the development of clinical signs of TTP in USS. In this regard, we are carefully following the clinical signs of KI's father. These 3 families also appear to show autosomal recessive inheritance of USS.

Regarding the inhibitor against vWF-CPase, it was detected neither in the plasmas nor the purified IgGs of the 3 USS patients in this study. The dramatic rise in the platelet count after each FFP infusion in the these patients also supports the absence of a vWF-CPase inhibitor.

The half-life of plasma vWF-CPase activity after plasma exchange in 2 brothers with CR-TTP was reported to be 2.1 to 3.3 days [18]. In the present ST and SY cases, the maximum increment of that vWF-CPase activity after FFP infusion was merely 7% to 8%, and it became less than 3% after 2 days. The reason for these 2 different findings has not been addressed.

The mechanism of thrombocytopenia and MAHA in USS is not fully elucidated. However, based on the recent theory of high shear-stress induced platelet aggregation [24], UL-vWFM, produced in vascular endothelial cells and released into circulation upon stimulation, appears to play a critical role, because plasma UL-vWFM is transported to peripheral small arteries, where high shear-stress is continuously generated [25]. Under these circumstances the "unactivated" UL-vWFM may change its molecular conformation to the activated form [26], to which vWF-CPase is most accessible [11]. However, in USS patients, vWF-CPase is totally defective, therefore, the activated UL-vWFM will interact with platelets and generate a signal to activate self-platelets; endogenous ADP released from platelets also accelerates the platelet activation [24]. A series of these reactions leads to formation of platelet microaggregates, resulting in thrombocytopenia. The clinical picture in USS patients is often dramatically exacerbated by a cold or a tiny acute inflammation [22], suggesting that some inflammatory cytokines augment the vWF release from endothelial cells over vWF-CPase that might be the trigger. As to why platelet count regularly drops at 2 to 3 weeks after FFP infusion, we assume that a specific time interval is required for UL-vWFM to accumulate in the plasma to a certain level at which clinical signs develop, even though UL-vWFM is partially destroyed by a small amount of vWF-CPase in FFP. Thus, USS patients do not usually require plasma exchange, and a simple supplementation of vWF-CPase by FFP infusion every 2 to 3 weeks is justified to prevent TTP, unless patients develop the inhibitor against vWF-CPase. Finally, it is suggested that USS should be used as a synonym for congenital TTP, and CR-TTP should refer to acquired TTP with a chronic relapsing clinical course.

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