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SEVERE VON WILLEBRAND'S DISEASE WITH ABNORMAL PLATELET AGGREGATION. A. Ihara(1), Y. Kobayashi(1), Y. Aramitsu(1), Y. Hara(2), K. Fujimura(2), A. Kuramoto(2). Department of Medicine and Pediatric, Kure National Hospital, Kure, Japan(1), Research Institute for Nuclear Medicine and Biology, Hiroshima Univ. Hiroshima, Japan(2).

A 17-year-old boy with a life long history of easy bruising, epistaxis, subcutaneous hematoma and prolonged bleeding time from minor injuries, was initially diagnosed as having von Willebrand's disese, when he presented epistaxis at 2 years of age. Since his initial diagnosis, he has been treated with cryoprecipitate on many occasions to correct his bleeding tendency. The laboratory findings in the patient and his family are summarized in the table. The patient's mother, father and one brother have not complained any bleeding tendency.

	Bleeding time Duke(min)	VIII:C %	vWF:Ag %	RCoF %	RIPA	Platelet aggregation
propositus	>30	9	<12.5	5	Abn.	Abn.
mother	4.5	100	45	88	N	N
father	2	100	110	104	N	Abn.
brother	5.5	100	112	100	N	N

Multimeric analysis of vWF using SDS agarose gels showed absence of large multimer in the patient's plasma, decreased large multimer in mother's and brother's plasma. When the patient's PRP was tested for aggregation and release of ATP by ADP, epinephrine and collagen, using lumi aggregometer, platelet aggregation was abnormal as shown by disaggregation and almost no ATP activity was detectable in the supernatant. ATP contents of patient's and father's platelet was about 50% of normal platelets. Washed platelets of the patient in normal plasma did not aggregate normally, but washed normal platelets in the patient's plasma aggregate normally. No inhibitor of vWF could be demonstrated in the patient's plasma. Clot retraction was normal. These findings suggest that our patient has inherited vWD from mateal side and the platelet aggregation defect, probably a kind of storage pool disease, from the paternal side of the family.

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HYPOTHYROIDISM AND ACQUIRED VON WILLEBRAND'S DISEASE
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A diagnosis of type IA von Willebrand's disease was made in three patients presenting with a mild bleeding tendency. Previously unrecognised hypothyroidism was also confirmed in two patients. In the third, hypothyroidism was diagnosed four years after initial presentation. In all three patients, thyroxine therapy was associated with correction of the haemostatic defect and resolution of the bleeding tendency. The association of von Willebrand's disease and hypothyrodism prompted us to examine the relationship between thyrotrophin (TSH), T_3, T_4 and components of the factor VIII complex in 12 patients with clinical and biochemical hypothyroidism. Factor IX was also studied. Mean VIII:C (measured by 2 stage assay) was 0.90 u/ul (range 0.55 - 1.14); mean vWF:Ag 0.83 u/ul (range 0.44 - 1.64); mean VIII:Rcof 0.75 (range 0.45 - 1.55); mean factor IX 0.72 (range 0.39 - 1.19). Multimeric analysis of vWF:Ag performed in samples from 8 patients was normal. VIII:Rcof levels were significantly lower than those of normal controls. A significant inverse correlation was obtained between TSH and factor IX and T_4 and vWF:Ag. Although there is a definite inverse relationship between TSH and factor IX, this is not evident with respect to factor VIII and a different mechanism is probably responsible for the modest reduction of vWF:Ag and the occurrence of clinically-evident von Willebrand's disease which we have demonstrated in a small proportion of hypothyroid patients.

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ABSENCE OF A BLEEDING TENDENCY IN SEVERE ACQUIRED DEFICIENCY OF PLASMA VON WILLEBRAND FACTOR (vWf)/F.VIII WITH NORMAL PLATELET vWf/F.VIII INDICES. J. Drouin (1), D. Lillicrap (2), A.R. Giles (2), C.A. Izaguirre (1), S. Windsor (2), and H. Hoogendorn (2). Department of Medicine, Ottawa General Hospital, Ottawa, Ontario, Canada (1), and Department of Pathology, Queen's University, Kingston, Ont., Canada (2).

A 67 year old male with IgA myeloma has been investigated for a severe deficiency of plasma vWf/F.VIII but normal platelet vWf/F.VIII. He has no personal history nor family history of bleeding problems. He was initially investigated for a prolonged APTT of 43 secs. (25-40) obtained in a preoperative clotting screen. During this investigation he was found to have IgA myeloma. In retrospect, an APTT prior to uneventful coronary artery bypass surgery two years previously had been prolonged. Routine investigation has shown that platelet count and bleeding time have been repeatedly normal. Plasma F.VIII:C is 0.08 u/ml., F.VIII:Cag 0.07 u/ml., vWf:Ag 0.05 u/ml. and ristocetin cofactor 0.05 u/ml. In contrast, platelet values for vWf:Ag of 53 units/10^9 platelets and F.VIII:Cag of 176 units/10^9 platelets are within the normal ranges for our laboratory. The platelet lysate vWf multimer pattern is also normal. Patient's plasma shows inhibitory activity against vWf:Ag but not against either F.VIII:C or ristocetin cofactor activity. When patient plasma is incubated for 60 mins at 37°C with vWf and analysed by crossed immunoelectrophoresis (CIE) for vWf:Ag, a double arc precipitin line is observed with marked retardation of the first arc. A similar vWf:Ag CIE double precipitin arc is seen following the infusion of cryoprecipitate. T 1/2 for F.VIII:C and vWf:Ag are both reduced following the infusion of cryoprecipitate - F.VIII:C 2 hrs, vWf:Ag 3 hrs. No secondary rise in F.VIII:C is seen at 24 hrs. Despite severe deficiency of plasma vWf/F.VIII, this man does not have a clinical bleeding tendency. We postulate that his plasma vWf/F.VIII deficiency is the result of complexing of his IgA myeloma protein with vWf, resulting in premature clearance of the vWf/F.VIII complex. This case further emphasizes the role of platelet associated coagulation factors in maintaining normal haemostasis.

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BLEEDING TIME IN TREATED PATIENTS WITH SEVERE VON WILLEBRAND DISEASE IS NOT CORRECTED ONLY BY GIVING NORMAL MULTIMERIC PLASMA VON WILLEBRAND FACTOR. P.M. Mannucci (1), M. Moia (1), D. Altieri (1), J. Monteagudo (2), R. Castillo (2). A. Bianchi Bonomi Hemophilia and Thrombosis Centre, Univ. Milano, Italy (1) and Servicio Hemoterapia y Hemostasia, Hopital Clinico y Provincial, Univ. Barcelona, Spain (2).

Even though it is generally held that cryoprecipitate (cryo) and fraction I-0 correct the prolonged bleeding time (BT) in patients with von Willebrand disease (VWD), perusal of reported data indicates that the correction is usually short lasting and often partial. We decided to do a controlled study of the relationship between the multimeric structure of von Willebrand factor (VWF) in 5 patients with severe VWD after infusion of three plasma concentrates : "wet" cryo, lyophilized (lyo) cryo, and fraction I-0 given in random order. The dosage of concentrates was tailored to achieve post infusion levels of RiCof above the lower normal limit (50 U/dL) for at least 3 hours. The post-infusion BT values are shown in the table.

	Bleeding time (min.)				
patients	BBB	ZG	CE	TA	DPE
WET CRYO	5	28.5	24	15	7
LYO CRYO	14	>30	13	16.5	>30
FRACTION I-0	15	>30	>30	12	>30

These findings indicate that the attainment of a normal BT is the exception rather than the rule after infusion of three plasma fractions used for treatment of severe VWD. In all the concentrates the proportions of large VWF multimers, calculated by scanning the electrophoretic gels, were the same as in normal standard plasmas. An intact multimeric structure was recovered in post-infusion plasma of patients treated with wet cryo, whereas there was post infusion loss of large multimers after lyo and fraction I-0. In conclusion, an intact multimeric structure in post infusion plasmas is necessary but not sufficient to sustain a normal BT in VWD patients.