CONCISE REPORT

Type IIB von Willebrand’s Disease: Differential Clearance of Endogenous Versus Transfused Large Multimer von Willebrand Factor


The abnormal multimeric composition of plasma von Willebrand factor in type IIB von Willebrand’s disease is transiently corrected after infusion of 1-deamino-[8-D-arginine]-vasopressin (DDAVP). However, the larger multimers released into the circulation disappear more rapidly in these patients than in type I von Willebrand’s disease or normals. We demonstrate that the larger multimers of normal von Willebrand factor transfused into a type IIB patient are cleared from the circulation more slowly than multimers of similar size endogenously released from tissue stores. The rate of disappearance of large von Willebrand factor multimers after infusion of cryoprecipitate is similar in IIB, IIA, and severe homozygous-like von Willebrand’s disease. Platelets from the IIB patient exhibited normal ristocetin-induced binding of normal von Willebrand factor. However, like normal platelets, they bound IIB von Willebrand factor at lower ristocetin concentrations than required for normal von Willebrand factor. These findings provide evidence that absence of the larger multimers from IIB plasma is related to a molecular abnormality of von Willebrand factor rather than to enhanced affinity of abnormal tissue or cellular binding sites, as is the case in the recently described “pseudo” von Willebrand’s disease and “platelet-type” von Willebrand’s disease.

TYPE IIB is a recently described form of von Willebrand’s disease (vWD) characterized by lack of the larger multimers of von Willebrand factor (vWF) in circulating blood.1-3 In contrast, all the multimeric forms are present in platelets as in normal controls.4 Following infusion of 1-deamino-[8-D-arginine]-vasopressin (DDAVP), a transient correction of the abnormal multimeric pattern of plasma vWF is observed.4 This has led us to postulate that the relative absence of large vWF multimers in IIB plasma is the result of rapid removal following release from tissue stores.2,4 Indirect evidence that this may be related to an intrinsic abnormality of the vWF molecule was derived from in vitro observations of increased affinity of IIB vWF for platelet binding sites in the presence of ristocetin.1,2 However, the results obtained in vivo after DDAVP infusion could also be explained by abnormalities of tissue and/or cellular binding sites rather than of the molecule itself. This possibility is suggested by the recent description of “pseudo” vWD5 and “platelet-type” vWD6 in which platelets exhibit increased affinity for vWF.

In this article we describe the results obtained in a IIB vWD patient after treatment with DDAVP or infusion of cryoprecipitate. The slower disappearance of larger normal vWF multimers transfused with cryoprecipitate, as compared with those endogenously released, favors the hypothesis of an intrinsic vWF abnormality in IIB vWD, rather than enhanced affinity of abnormal cellular or tissue binding sites.

MATERIALS AND METHODS

Patients

The patient with IIB vWD studied here has been previously characterized in detail (family 3, patient 13’). Infusion of DDAVP (a drug licensed in Italy for the treatment of vWD, trademark: Minirin, Valeas, Milan) was performed on an experimental basis to which the patient gave her informed consent. This experiment was performed according to the Declaration of Helsinki. The infusion of 30 bags of single-donor blood bank cryoprecipitate in the same patient was required to perform surgery for a skin neoplasia. The patient with IIA vWD studied here has also been previously characterized (family 10, patient 28’). Infusion of cryoprecipitate (30 bags) in this patient was necessary for treatment of prolonged bleeding after tooth extractions. Normal controls were healthy volunteers from the Policlinico Hospital staff.

Methods

DDAVP was infused at the dose of 0.4 µg/kg of body weight according to a protocol previously described.4 Blood was collected and processed to prepare platelet-rich and platelet-poor plasma as reported.4 Analysis of vWF multimeric distribution was performed as previously described in detail.4,4 Platelets were washed free of plasma constituents with the albumin density gradient technique of Walsh et al.3 Binding of vWF to platelets in the presence of ristocetin was evaluated as previously reported.1,2

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RESULTS

Administration of DDAVP to the patient with IIB vWD produced a rapid appearance of larger vWF multimers in plasma, and the abnormal basal pattern was transiently normalized (Fig. 1). There was a threefold increase of circulating vWF, but the bleeding time was only slightly shortened and remained longer than 15 min. In accordance with previously reported findings, the disappearance from plasma of the DDAVP-released larger forms was more rapid than in normal and type 1 vWD. None of the larger vWF multimers could be detected in the IIB patient 2 hr after infusion of DDAVP (Fig. 1). Infusion of cryoprecipitate in the same patient increased vWF plasma levels 3–4-fold over basal values, and the multimeric structure was normal 5 min after the end of infusion (Fig. 2). Bleeding time at the same time was 12 min. In contrast with the findings after DDAVP, the larger multimers of infused vWF were still detectable 7 hr after administration of cryoprecipitate (Fig. 2). Bleeding time at that time was 9.5 min. Partial clearing of the large vWF multimers was evident after 24 hr (Fig. 2). In this IIB patient, in vivo survival of large normal vWF multimers infused with cryoprecipitate was similar to that observed in a IIA patient (Fig. 3) and in five patients with severe homozygous-like vWD (not shown). Shortening of bleeding time and control of bleeding was achieved in all the patients infused with cryoprecipitate, though this was not true with DDAVP.

Washed platelets from the patient with IIB vWD behaved like normal platelets in binding normal vWF in the presence of ristocetin (Fig. 4). However, both normal and IIB platelets bound IIB vWF at lower ristocetin concentrations than necessary for normal vWF (Fig. 4). Similar results (not shown here) were obtained in two additional patients from the same family and in two patients from another family with type IIB vWD.

DISCUSSION

Disappearance of the larger vWF multimers released into the circulation after infusion of DDAVP occurs more rapidly in type IIB vWD than in type I or normals. In this study we demonstrate that the larger multimers of normal vWF transfused into a patient with type IIB vWD have a longer survival in the circulation than multimers of corresponding size endogenously released from the patient’s tissue stores after DDAVP infusion. Clearing of the larger multimers transfused with normal cryoprecipitate was not faster in IIB than in IIA or in severe homozygous-like
vWD. Therefore, these findings provide in vivo evidence that the characteristic absence of larger molecular forms of vWF from IIB plasma is related to rapid removal of an intrinsically abnormal molecule after release from tissue stores, rather than to enhanced affinity of abnormal tissue or cellular binding sites. Based on these observations, cryoprecipitate from normal plasma is currently the most effective therapy for completely correcting the hemostatic abnormality in this subtype of vWD.

The recent descriptions of "pseudo" vWD\(^5\) and "platelet-type" vWD\(^6\) have suggested that there are individuals in which a platelet abnormality may be
responsible for increased binding of larger vWF multimers both in vivo and in vitro in the presence of ristocetin. That this was not the case in type IIB vWD was demonstrated by the survival studies of transfused normal vWF and by the demonstration that IIB platelets had the same affinity as normal platelets for normal vWF but increased affinity for IIB vWF in the presence of ristocetin.

In conclusion, the results of these studies provide evidence that the pathogenesis of IIB vWD is related to a molecular abnormality of vWF and is therefore distinct from "pseudo" or "platelet-type" vWD.

REFERENCES

Type IIB von Willebrand's disease: differential clearance of endogenous versus transfused large multimer von willebrand factor

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