Type IIA von Willebrand Disease With Apparent Recessive Inheritance

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Type IIA von Willebrand's Disease (vWD), defined by the absence or decrease of large multimers of von Willebrand factor antigen (vWF:Ag), has been divided into a number of subtypes, the most common being type IIA. In addition to the absence of large multimers, type IIA vWD is characterized by (1) a disparity in the amount of vWF:Ag and vWF activity as measured by ristocetin (RCO), with vWF:Ag greater than RCO; (2) the presence of a repeating five-band pattern of small multimers seen on 3.0% agarose gel electrophoresis, with relative increased density of the outermost flanking subbands as compared with normal; (3) normal or decreased RCO-induced platelet aggregation; and (4) little or no response to infusion of desmopressin. The inheritance of type IIA vWD has been dominant in 56 reported individuals in 26 families. In this report, we describe an individual with type IIA vWD with apparent autosomal recessive inheritance.

CASE REPORT

The propositus is an eight-year-old white female with history of an increased bleeding tendency since infancy. At the age of 2 months she bled for a day following her first immunization injection, and she was noted to have easy bruising following minor injuries. At the age of 2 years, she was seen in the emergency room because of four days of bleeding from a tongue laceration. The diagnosis of vWD was made at this time based on the prolonged bleeding time and decreased levels of factor VIII coagulant (46%), vWF:Ag (40%), and RCO (<1%). Two-dimensional crossed-immunoelectrophoresis of vWF:Ag revealed an abnormal fast-moving component. The child subsequently has had repeated bleeding episodes following minor injuries and has received cryoprecipitate for treatment of a laceration and for a tooth extraction. More recently she received antifibrinolytic therapy and an infusion of desmopressin in preparation for a tooth extraction, and hemostasis was satisfactory. Her family history is negative for bleeding manifestations. Both parents and three siblings (6, 14, and 16 years) are living and well, and all members of the family were evaluated.

MATERIALS AND METHODS

Computations of bleeding times were performed by the Ivy method. Blood collection, plasma preparation and storage, as well as methods for factor VIII coagulant activity (one-stage partial thromboplastin time method), vWF:Ag (Laurell), multimer analysis (sodium dodecyl sulfate agarose electrophoresis using 1.5% and 3.0% gels), and RCO (macroscopic agglutination technique using formalin-fixed platelets) have been described previously. The inheritance of type IIA vWD has been dominant in 56 reported individuals in 26 families. In this report, we describe an individual with type IIA vWD with apparent autosomal recessive inheritance.

RESULTS

The results of plasma studies of the propositus, her parents, and three siblings are shown in Table 1. The propositus had a prolonged bleeding time (>20 minutes), significantly decreased vWF:Ag (22%) and RCO (3%), and normal RIPA. The only abnormality noted in the parents and siblings was a uniformly decreased amount of RCO in relation to vWF:Ag. The ratios of RCO to vWF:Ag for the parents and siblings were 0.47, 0.60, 0.49, 0.61, and 0.67 (mean, 0.57). For comparison, mean ratios of RCO to vWF:Ag in normal individuals and other vWD subjects studied in our laboratory are as follows: normals (26), 1.02; type I vWD (15), 1.21; type IIA (14), 0.51, and type IIB (9), 1.19.

The multimer patterns of vWF:Ag on 1.5% and 3.0% agarose gel electrophoresis are shown in Fig 1A and B. On 1.5% gel the propositus lacks large and intermediate multimers, whereas her parents and siblings all have normal patterns. On 3.0% gel the propositus has a repeating five-band pattern of small multimers with a relative increase in the density of the outermost flanking subbands. The subband patterns of the parents and siblings all appear normal.

Infusion of desmopressin (0.3 µg/kg) into the propositus...
Fig 1. SDS agarose gel electrophoresis of vWF:Ag on 1.5% (A) and 3.0% (B) gels. From right to left the lanes are normal plasma, propositus, mother, father, brother 1, brother 2, and sister. On 1.5% gel, the propositus lacks large and intermediate multimers. whereas the other family members have normal patterns. On 3.0% gel, the propositus has a repeating five-band pattern of small multimers with an increase in density of the outermost flanking subbands of the small multimers, and other family members have normal patterns.

resulted in increases of factor VIII coagulant activity (18% to 128%) and vWF:Ag (23% to 114%), whereas RCo only increased from 3% to 17%. Plasma vWF:Ag multimers were analyzed before and after desmopressin infusion in the propositus; patterns are shown in Fig 2. On 1.5% gel only a few of the smaller intermediate multimers appeared following desmopressin infusion. An increase in density of the smallest multimers was noted on 3.0% gel.

REFERENCES

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