

TWO VARIANTS OF CANINE VON WILLEBRAND'S DISEASE. W. Jean Dodds and Roger E. Benson. Division of Laboratories and Research, New York State Department of Health, Albany, New York, U.S.A.

Previous studies in our laboratory have characterized von Willebrand's disease (VWD) in three families of dogs: German shepherds, miniature schnauzers, and golden retrievers (Blood, 45, 221, 1975; Thromb. Res., 7, 383, 1975). In each family the disease follows a classical pattern of autosomal inheritance; reduced factor VIII activity, factor VIII-related antigen (FVIII-RA), platelet retention and ristocetin-induced platelet aggregation; and long bleeding times; although the severity of expression varies between the breeds. Two new families currently being studied (Doberman pinschers and Scottish terriers) deviate significantly from this expected pattern. Several severely affected dogs, presumed homozygous by virtue of having two affected parents and undetectable FVIII-RA, have factor VIII activity between 20-50% of normal. Even more unusual is that mildly affected or clinically normal close relatives of these dogs have low-normal or normal factor VIII activity but very low FVIII-RA (5-25%). However, there are also severely affected dogs from both families with classic VWD including very low factor VIII activity (<10%) and undetectable FVIII-RA. The same monospecific rabbit anticanine factor VIII was used to quantitate and compare the FVIII-RA levels of affected and normal members of all five dog families. The explanation for finding low antigen levels in conjunction with normal biologic activity in families where complete expression of the disease coexists remains obscure.

Published online: 2019-04-16

REDUCED ANTIGENIC REACTIVITY IN "VARIANTS" OF VON WILLEBRAND'S DISEASE. N. Ardailiou, J.P. Girma, I. Shoa'i, J.-M. Laverne, D. Meyer and M.J. Larrieu. Institut de Pathologie Cellulaire, Hôpital de Bicêtre, Paris, France.

Factor VIII related antigen (FVIII:AG) was measured in 49 cases of von Willebrand's disease (vWd) by an immunoradiometric assay (coated tube system), using purified IgG prepared from antisera raised in both a rabbit and a goat. The control dose-response curve showed a linear relationship between bound radioactivity and log plasma dilutions between 1:25,000 and 1:400. At higher concentrations of plasma (i.e. lower dilutions), the percentage of bound radioactivity reached a plateau. In severe cases of vWd, no measurable FVIII:AG ( $<1.10^{-4}$  u/ml) was detected. Most of the other patients had a normal response pattern with reduced levels of antigen. This contrasted with 13 patients who showed an abnormal dose-response curve. In all 13 cases, the maximal percentage of bound radioactivity (plateau) was lower than in the normal. These patients had a 20-30% absolute reduction of antibody binding capacity. This phenomenon was obtained with both rabbit and goat antibody. In addition, 4 of these patients (from 2 families) showed a lack of parallelism to the normal in the linear portion of their dose-response curve. This lack of parallelism only occurred with the rabbit and not with the goat antibody. All of these 13 patients fulfilled the criteria for "variants" of vWd, i.e. abnormal electrophoretic mobility and a disproportionately reduced Willebrand Factor activity in comparison to FVIII:AG. These abnormalities of the immunoradiometric response are further evidence that an abnormal protein with reduced antigenic reactivity is present in "variants" of von Willebrand's disease.

CHARACTERISTICS OF FACTOR VIII RELATED PROTEIN IN DIFFERENT TYPES OF VON WILLEBRAND'S DISEASE. A.L. Bloom and I.R. Peake. University Hospital of Wales, Cardiff, U.K.

The antigenic, biochemical and biological reactions of factor VIII related protein were studied in normal plasma and in the plasma of patients with different types of von Willebrand's disease (vWd). Antigenic reactivity was compared using the Laurell electroimmunoassay (LA) and an immunoradiometric assay (IRMA). Biochemical characteristics of factor VIII related antigen (FVIIIIRAG) were compared by examining its electrophoretic mobility (EM) on two dimensional crossed immunoelectrophoresis (2DCIE) and by determining its precipitation properties with the glycoprotein precipitant concanavalin A (Con A). Biological reactions were compared using the ristocetin cofactor (RiCoF) assay on fixed platelets and by determining procoagulant factor VIII (FVIIIIC). In normal plasma the levels of FVIIIIRAG measured by LA correlated with the IRMA and dose response curves were parallel. At a concentration of 1mg/ml Con A completely precipitated FVIIIIRAG. The biological activities, RiCoF and FVIIIIC, were normal and correlated with those of FVIIIIRAG. In patients with vWd in whom levels of FVIIIIRAG by LA were normal the EM by 2DCIE was increased. In these patients the dose-response curves of the IRMA were not parallel to normal, FVIIIIRAG was not precipitated normally by Con A and the RiCoF activity was reduced. Similar findings were observed in some patients with "typical" intermediate vWd in whom the plasma levels of FVIIIIRAG were too low to determine EM. In other patients with vWd the dose response curves of the IRMA were parallel. The results suggest that the non-parallel dose response curves of the IRMA were due to the presence of abnormal FVIIIIRAG and were consistent with variations of antigenic reactivity or binding sites in these patients.