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VON WILLEBRAND DISEASE

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INTRODUCTION

Von Willebrand disease (VWD) is the most common congenital bleeding disorder. It is estimated to occur at a frequency of one in 100 individuals, but is symptomatic in only about one in 10,000. Von Willebrand disease is caused by mutations in von Willebrand factor (VWF). The gene for von Willebrand Factor is located on chromosome 12, and the disease is inherited in an autosomal manner, affecting both males and females. Von Willebrand factor is a glycoprotein consisting of disulfide-linked high molecular weight multimeric FVIII proteins (multimers), and is synthesized in megakaryocytes and endothelial cells, and stored in platelets and endothelial cells. Von Willebrand factor serves as a carrier protein for FVIII and promotes platelet aggregation after vessel injury.

Von Willebrand disease is a clinically heterogeneous disease with a number of disease variants, each characterized by different quantitative and/or qualitative defects in von Willebrand factor. It is import to determine the specific von Willebrand disease variant in order to establish the best and safest treatment for each patient.

Recently a revised simplified classification system for von Willebrand disease was proposed by the international Society of Thrombosis and Hemostasis (ISTH) (Sadler JE. Thromb Hemostas 1994; 71:520). The new classification was prompted by recent progress in defining VWF mutations causing disease, and simplifies the disease into six disease categories from over 30 previously recognized (see below).

COAGULATION DEFECTS IN VON WILLEBRAND DISEASE

Mutations in von Willebrand factor result in deficient or defective von Willebrand factor antigen and von Willebrand factor activity (ristocetin cofactor). These are usually accompanied by a decrease in FVIII coagulant activity (FVIII:C), because normal expression of FVIII:C in the circulation is dependent

on FVIII:C complexing with its carrier protein, von Willebrand factor. The coagulation screening tests typically associated with the defects in von Willebrand factor and FVIII:C include a prolonged activated partial thromboplastin time (APTT) and a long bleeding time.

In some von Willebrand disease variants (see below) the von Willebrand multimers are qualitatively normal but quantitatively decreased, while in other variants the von Willebrand multimers are both qualitatively and quantitatively abnormal. Because there is temporal variability in these coagulation tests, the clinical history is very important in diagnosis of von Willebrand disease.

CLINICAL ASPECTS OF VON WILLEBRAND DISEASE

Von Willebrand disease was first recognized by Erik von Willebrand in 1926 in related kindreds living in the isolated Aaland Islands in the North Sea near Finland. Von Willebrand disease was first termed 'pseudohemophilia', because it differed from hemophilia in its primarily mucosal (rather than joint and muscle) bleeding, the prolonged bleeding time (not found in hemophilia), and the fact that it affected females (hemophilia is X-linked and affects primarily males).

Symptoms in individuals with von Willebrand disease include easy bruising, epistaxis, postoperative or post-traumatic bleeding, and mucosal bleeding, primarily in the gastrointestinal and genitourinary tracts. Females with severe disease may also suffer menorrhagia. The clinical bleeding in von Willebrand disease occurs because the defective von Willebrand factor results in defective platelet aggregation and platelet plug formation following vessel injury.

CLASSIFICATION OF VON WILLEBRAND DISEASE

The type of mutation affecting the von Willebrand factor locus forms the basis for classification of von Willebrand disease. By convention, there are three major types; Type II is subdivided into four different subtypes.

- Type 1, which occurs in approximately 70% of affected patients, is characterized by a mild to moderate deficiency in qualitatively normal von Willebrand factor. There is a parallel decrease in FVIII:C and in autosomal dominant disease.

- Type 2, which is found in 15-30%, is characterized by a qualitative abnormality in von Willebrand factor. There is an absence of the high molecular weight multimers. It is inherited both as an autosomal

dominant and recessive disease. Type II is further subdivided into four different groups: 2A, 2B, 2M, 2D.

- Type 2A is characterized by a loss of large molecular weight multimers. These are required for platelet adhesion during primary hemostasis.

- In Type 2B disease, there is increased binding of von Willebrand factor to platelets. This results in hyper-aggegable platelets. In vitro, this defect can be demonstrated by platelet aggregation with half strength (0.5 mg/ml) ristocetin; platelets from normal individuals or those with the other forms of von Willebrand disease will not aggregate in this system. It is important to distinguish this type of von Willebrand's disease because one of the standard treatments, DDAVP (see below), may act to further enhance platelet aggregation and worsen the thrombocytopenia. Because of these problems, DDAVP is contraindicated in Type 2B von Willebrand's disease.

- Type 3, which occurs in <1% of patients with von Willebrand disease, is characterized by a complete deficiency of von Willebrand factor. This type is inherited as an autosomal recessive disease, and, as such, is the severest form of the disease. Multimers, von Willebrand factor antigen, von Willebrand factor activity, and FVIII:C are usually undetectable. The bleeding time is usually greater than 15 minutes.

GENETICS OF VON WILLEBRAND DISEASE

Von Willebrand factor is encoded by an autosomal gene on chromosome 12. Quantitative deficiency of von Willebrand factor, such as which occurs in Type 1 and 3 von Willebrand disease, has been associated with promoter, nonsense, and frameshift mutations, with large deletions. Qualitative deficiency of von Willebrand factor, such as occurs in Type 2 von Willebrand disease, has been associated with missense mutations and small deletions or insertions.

It is anticipated that as mutations in von Willebrand factor continue to be identified, newer approaches to prevention of postoperative vascular occlusion and atherosclerotic plaques may be developed, taking advantage of the interference in primary hemostasis afforded by mutations in von Willebrand factor.

TREATMENT OF VON WILLEBRAND DISEASE

Cryoprecipitate contains the high molecular weight von Willebrand factor multimers missing in von Willebrand disease, and could theoretically be the treatment for all types of von Willebrand disease. However, it is not the preferred treatment for von Willebrand disease, because cryoprecipitate (as a cold precipitate of plasma) cannot be inactivated or purified without destroying the activity, and thus transmission of HIV and/or hepatitis viruses cannot be prevented with this product; other than by standard antibody screening.

The recommended treatment for Type I von Willebrand disease or other clinically mild disease is DDAVP, an arginine vasopressin analogue. DDAVP serves to release von Willebrand factor from storage in Weibel Palade bodies in endothelial cells and alpha granules of platelet. The standard dose is 0.3 µg per kilogram body weight, and DDAVP may be given once daily. DDAVP is not helpful for individuals with severe disease, as there is little or no von Willebrand factor in storage sites. In general, DDAVP is well-tolerated, with occasional flushing during infusion. The greatest drawback to its use is the development of tachyphylaxis after two or three treatments. As mentioned above, DDAVP is contraindicated for individuals with 2B disease, because it may further increase platelet aggregation and thrombocytopenia.

For individuals with moderate to severe von Willebrand disease, such as those with Type 3 von Willebrand disease or severe Type 2A variants, the blood product of choice is factor VIII concentrate containing high-molecular weight von Willebrand factor multimers, e.g. Humate P. This clotting factor concentrate is virally-inactivated by pasteurization and highly purified by the use of monoclonal antibody purification. The standard dose for a hemorrhage is 25 to 40 units per kilogram of body weight, administered once or twice daily, depending on the severity of the hemorrhage. There is no evidence for transmission of hepatitis or HIV virus with this product, and the only drawback to its use is the potential transmission of non-lipid-enveloped viruses, such as hepatitis A or parvovirus.

As with other congenital coagulation disorders, the use of hepatitis B vaccine for prophylaxis against potential hepatitis B transmission, and oral antifibrinolytic agents, such as Amicar, for oral bleeding or tooth extraction, are recommended.

SUMMARY

Von Willebrand disease is a heterogeneous bleeding disorder, characterized by deficiency in a glycoprotein, von Willebrand factor, VWF, which is important in platelet plug and fibrin clot formation when injury occurs. Coagulation findings include a prolonged bleeding time and decreased FVIII activity, von Willebrand factor, and ristocetin platelet aggregation. Mucosal bleeding is the most typical clinical symptom, occurring primarily in the oral, gastrointestinal, and genitourinary tracts. Treatment of von Willebrand disease is with DDAVP for mild or moderate disease, and with Humate P for severe disease or Type 2B variants. Current research on mutations in von Willebrand factor and its regulatory sequences may lead to new approaches to the prevention of vascular occlusion and atherosclerotic vascular disease.

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