Understanding the epidemiology and diagnosis of Von Willebrand disease.

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Introduction

Most commonly inherited bleeding disorder, first described in Aland Islands by Erik von Willebrand. It occurs as a result of decrease in plasma levels or defect in von Willebrand factor which is a large multimeric glycoprotein. Monomers of this glycoprotein undergo N-glycosylation to form dimers which get arranged to give multimers. Binding with plasma proteins (especially factor VIII) is the main function of von Willebrand factor. The disease is of two forms: Inherited and acquired forms. Inherited forms are of three major types. They are type 1, type 2, and type 3; in which type 2 is sub-divided into 2A, 2B, 2M, 2N. Type 1 is more prevalent than all other types. Mucocutaneous bleeding is mild in type 1 whereas it is mild to moderate in types 2A, 2B, and 2M. Type 2N has similar symptoms of haemophilia. The pathophysiology of each type depends on the qualitative or quantitative defects in von Willebrand factor. The diagnosis is based on von Willebrand factor antigen, von Willebrand factor activity assay, FVIII coagulant activity and some other additional tests. Results should be analyzed within the context of blood group. Von Willebrand factor multimer analysis is essential for typing and sub typing the disease. The management of the disease involves replacement therapy, non-replacement therapy and other therapies that include antifibrinolytics and topical agents [1].

When a blood vessel is injured and starts bleeding, platelets together with some clotting factors form a plug at the region of injury. As a result, the blood vessel stops bleeding. The plasma protein which allows or helps the platelets to stick with each other and form a clump is the von Willebrand factor (VWF). It also carries factor VIII. When there is a decrease in plasma levels or defect in the von Willebrand factor, the ability of the blood to clot decreases leading to a heavy and continuous bleeding after an injury which is termed as von Willebrand disorder or disease (VWD). This may cause internal organ damage and rarely may lead to death [2].

VWD is the most commonly inherited bleeding disorder. Although it is a form of haemophilia which is also a clotting disorder, haemophilia is mostly due to the deficiency of clotting factors. For instance, haemophilia A is due to factor VIII deficiency and haemophilia B is due factor IX deficiency. VWD is milder and common when compared to haemophilia.

Von Willebrand factor

Von willebrand factor (VWF) is a large multimeric glycoprotein present in plasma. It is synthesized in Weibel-Palade bodies in endothelium, α-granules of platelets (megakaryocytes) and sub-endothelial connective tissue.

Functions: As already mentioned, the specific domains present in it are responsible for its functions. The main function is to bind with plasma proteins, especially factor VIII and coagulate blood. Factor VIII in its inactive state binds to VWF in the circulation. If it is unbound, it rapidly degrades. When VWF is exposed in endothelium during an injury to blood vessel, it binds to collagen. When coagulation is stimulated, the platelet receptors get activated. VWF binds to these activated receptors. VWF binds to platelet glycoprotein Ib (GPIb) receptor when it forms a complex with glycoprotein IX (GPIX) and glycoprotein V (GPV). This occurs when there is a rapid flow in narrow blood vessels. Studies show that VWF uncoils and decelerate platelets under these conditions [3].

Catabolism: A disintegrin-like and metalloprotease domain with thrombospondin type 1 motifs (ADAMTS-13), a plasma metalloprotease breaks down VWF between tyrosine at position 842 and methionine at position 843 in A2 domain. As a consequence, the multimers are broken into smaller sub-units which can be degraded by other peptidases

Epidemiology

The disease prevalence is about only 1%. More often, it can be detected in women based on the bleeding tendency during menstruation. The disease may be severe in people with 'O' blood group. Type 1 includes 60%-80% of the cases. Type 2 includes 20-30%. Type 3 accounts for less than 5% of all the cases. Acquired VWD occurs most often in individuals over 40 years with no prior bleeding history.

Classification

These are of two forms. They are: Inherited forms and acquired form. Hereditary forms include three major types and a platelet type. The three major forms are type 1, type 2, and type 3. The international society of thrombosis and homeostasis has classified VWD based on the definition of qualitative and quantitative defects. According to this classification, type 2 VWD is again classified into four different types like type 2A, type 2B, type 2M and type 2N.

Aetiology

It is an inherited disease where the parent carrying the gene may or may not be symptomatic. Type 1 and type 2 are inherited if the gene is passed on to the offspring from either

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of the parent. Type 3 is inherited only if the gene is passed from both the parents. Acquired VWD is seen in patients with auto antibodies.

Clinical Manifestations

Children with VWD may have symptoms that are different from those of parent carrying the gene. It is the bleeding disorder that is commonly seen in women. Menorrhagia is seen in more than 70% of women with VWD and a half suffers from dysmenorrheal. Different types of von Willebrand diseases have varying degrees of bleeding tendencies (nose bleeding, bleeding gums, easy bruising). Individual with type 3 VWD have a severe internal and joint bleeding, but this is very rare condition.

Typically type 1 VWD manifests mild mucocutaneous bleeding. Most common symptoms include bruising and epistaxis. Women experience a heavy menstrual bleeding in reproductive age and a heavy blood loss during delivery. If the VWF levels are lower than 15 IU/dl, the disease symptoms can be more severe. Type 2A VWD individuals usually manifest mild to moderate mucocutaneous bleeding. Whereas type 2B VWD typically have mild to moderate mucocutaneous bleeding. Thrombocytopenia may be observed which becomes worsened during stress (severe infection/surgery/pregnancy/ if desmopressin is used). Like type 2B individuals, type 2M VWD also typically has mild to moderate mucocutaneous bleeding. When there is a low or absent VWF:RCo, the episodes of bleeding can be severe. Type 2N VWD symptoms are similar to those of mild hemophilia A which includes excessive bleeding at the time of surgery. Acquired VWD individuals also present with mild to moderate bleeding [4].

Diagnosis

Type 1 and type 2 people do not have major bleeding problems. Hence, the early diagnosis is difficult. Whereas, early diagnosis is easy in type 3 people as they have severe bleeding problems since infancy. The diagnosis is established based on the personal and/or family history of abnormal bleeding and diagnostic test results. The screening tests like bleeding time and platelet function analyzer (PFA-100®, Dade Behring, Deerfield, I11) are less sensitive. Diagnosis is mainly based on VWF activity assay (VWF:RCo), reduced VWF antigen (VWF:Ag), and FVIII coagulant activity (FVIII:C). The various tests that are included in the diagnosis of VWD are: Bleeding history, total blood count, VWD profile testing (VWF:Ag, VWF:RCo, FVIII:C), ABO blood group. Optional tests if initial test results suggest VWD include: VWF multimer analysis, VWF: CBA, VWF: FVIIIB, RIPA, Genetic tests [5].

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