

Von Willebrand Disease

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ABSTRACT

Von Willebrand Disease (VWD) is a disorder of blood in which the proper clotting of the blood does not occur. Von Willebrand Factor (VMF) is an important multimeric glycoprotein of the blood that helps to stop the bleeding. When the function of this von Willebrand factor is impaired we can observe this Von Willebrand Disease. Usually, the VWF in the blood attaches to small blood cells called platelets when a person is injured and starts to bleed. In order to stop bleeding at the site of injury, this VWF helps the platelets stick together to form a clot by acting like a glue. In case of the patients with Von Willebrand Disease it is very difficult to stop the bleeding and is often life threatening. In this review, the symptoms, diagnosis and the treatment strategies were discussed. Health care professionals expertise in the haemostasis are required in the clinical scenario for better management of this disease. As it is an inherited disease, special care must be taken in evaluating the family history during the diagnosis and extensive research is still required for providing the better management and treatment.

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Introduction

Von Willebrand Disease (VWD) is a disorder of blood in which the proper clotting of the blood does not occur. Von Willebrand Factor (VMF) is an important multimeric glycoprotein of the blood that helps to stop the bleeding. When the function of this von Willebrand factor is impaired, we can observe this Von Willebrand Disease. Usually, the VWF in the blood attaches to the platelets when a person is injured and starts to bleed. In order to stop bleeding at the site of injury, this VWF helps the platelets stick together to form a clot by acting like a glue. In case of the patients with Von Willebrand Disease it is very difficult to stop the bleeding and is often life threatening [1].

Classification

VWF can be classified into two forms that include inherited form and acquired form. The inherited forms include three major types (type 1, 2 and 3) and a platelet type. Type 2 VWD is further classified into 4 different subtypes that include type 2A, 2B, 2M and 2N. VWD is a hereditary disease while the parents may or may not be symptomatic. Type 1 and Type 2 are inherited if either of the parents is affected while type 3 is inherited only if the genes are inherited from both the parents. Acquired VWD is prevalent among patients with auto antibodies. The prevalence of VWD is just 1%. VWD is highly prevalent in women based on the menstrual bleeding tendency and more severe in people with 'O' blood group. Type 1 VWD

accounts for 60% - 80% of the cases, type 2 accounts for 20-30% while type 3 accounts for less than 5% of all the cases. Acquired VWD occurs mostly among individuals over 40 years with no history of bleeding disorder [2].

Symptoms

The symptoms of VWD may vary among the children and their affected parents. VWD has a very high prevalence among women, menorrhagia is seen in about 70% of the women suffering from VWD while half of them suffers from dysmenorrhea. The intensity of the bleeding tendency varies based on the type of the disease (gum bleeding, bruising, nose bleeding). Type 1 VWD manifests the symptoms such as mucocutaneous bleeding, bruising, epistaxis, heavy menstrual bleeding in reproductive age and heavy blood loss during delivery. Type 2 VWD manifests mild to moderate symptoms such as mucocutaneous bleeding while type 2B and 2M VWD typically manifests mild to moderate mucocutaneous bleeding. Thrombocytopenia gets worsened during stress, severe infection, surgery and pregnancy. The symptoms of type 2N VWD are similar to those of mild hemophilia resulting in excessive bleeding during surgery. Severe internal bleeding and joint bleeding occurs in type 3 VWD which is a rare condition. Acquired VWD presents with similar manifestations as inherited VWD such as mild to moderate bleeding [3-6].

Diagnosis

Type 1 and type 2 VWD do not exhibit bleeding disorders making it more difficult for early diagnosis whereas, the early diagnosis is easy in patients with type 3 VWD as they suffer from bleeding disorders since infancy. The VWD diagnosis is done based on the personal & family history of bleeding disorders or abnormal bleeding and diagnostic results. Screening tests such as bleeding time and platelet function analyzer are less sensitive in VWD diagnosis. The diagnosis of VWF is done based on the VWF activity assay, FVIII coagulant activity and reduced VWF antigen. The various tests used in the diagnosis of VWD are: bleeding history, complete blood count, VWD profile testing, ABO blood group. If the initial tests suggest VWD, then the following optional tests such as VWF: Multimer Analysis, VWF: Collagen Binding Assay, Ristocetin Induced Platelet Aggregation, VWF: Factor VIII Binding Assay and Genetic tests can be suggested [7-10].

Treatment

Non-replacement therapy

Desmopressin is a synthetic derivative of antidiuretic, vasopressin and this drug stimulates the release of VWF from endothelial cells, through its agonistic effect on vasopressin V2 receptors. The plasma concentration of VWF is increased through their cAMP mediated release from the endothelial cell Weibel Palade bodies and also helps in elevating the FVIII levels. The tissue plasminogen activator released by the Desmopressin is rapidly inactivated by plasminogen activator inhibitor (PAI-1) thereby preventing excessive fibrinolysis or bleeding. Desmopressin is mostly indicated for individuals with type 1 VWD and some type 2 VWD, which can be given subcutaneously or intravenously or intranasally with a standard dose of 0.3mg/kg IV in 50ml of normal saline over 30 min. Desmopressin is not indicated for type 2B (as there is a fall in platelet count after its use) and type 3 VWD (no clinical relevant rise in FVIII or VWF:RCO) [11-13].

Replacement therapy

Humate - P® and Aplhanate SD/HT® are the plasma derived concentrates to replace VWF. These two products can't be interchanged with each other as they products are not identical to each other and their ratios may vary. Humate - P® is administered IV and is given for patients with desmopressin sensitivity or patients on prolonged therapy. It is used in treatment of any type 2 or severe type 3 VWD [14-16].

Antifibrinolytics

The majorly used antifibrinolytics in VWD therapy includes aminocaproic acid and tranexamic acid. These drugs act by inhibiting the plasminogen to plasmin conversion thereby preventing fibrinolysis and stabilizing the formed clots. The antifibrinolytics can be given either orally or IV in the treatment of mild to moderate mucocutaneous bleeding among VWD patients. Aminocaproic acid, adult dose is 4-5g (loading dose) given PO or IV 1 hour prior to invasive procedures which is followed by 1g/hr PO or IV or 4-6g for every 4-6 hours until the bleeding is controlled or 5-7 days to post operation. The maximum daily dose should not exceed 24g to minimize side effects [17,18].

Topical agents

Thrombin-JMI (topical bovine thrombin) is used in cases of minor capillary bleeding and venules. Fibrin sealant can also be used but, it is found to be ineffective in treatment of heavy bleeding. It is proved to be good as an adjuvant therapy in dental surgery in VWD patients. Topical collagen sponges are also found to be effective in controlling wound bleeding [19-21].

Conclusion

Health care professionals expertise in the haemostasis are required in the clinical scenario for better management of this disease. As it is an inherited disease, special care must be taken in evaluating the family history during the diagnosis process and extensive research is still required for providing the better management and treatment.

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