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Von Wille brand disease: An Overview

Inherited Bleeding disorder

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Abstract: Von Williebrand disease is a common autosomal inherited mucocutaneous bleeding disorder, It results from the quantitative or qualitative defects in plasma von Willebrand factor (VWF). The analysis of Phenotype and genotype in patients with the three VWD types have aided in the understanding of the Von Willi brand disease structure and function. The Research of the affected patients with vWD disease types has been determined mutations in up to 70% of type 1 and 100% of type 3 VWD cases. The Von Willi brand disease is divided into two forms that is inherited and acquired forms. Inherited forms are of three major types. They are type 1, type 2, and type 3 and type 2 is subdivided into 2A, 2B, 2M, and 2N. Type 1 is more frequent than all other types of disease. Mucocutaneous bleeding is mild in type 1 because it is mild to moderate in types 2A, 2B, and 2M. Type 2N has similar symptoms to hemophilia. The pathophysiology of vWD disease depends on the qualitative or quantitative defects in plasma von Willebrand factor in the blood. The diagnosis of the von Willi brand disease is based on von Willebrand factor antigen, and, FVIII coagulant activity, and some other additional tests. The Treatment of the von Willi brand disease involves different type of replacement therapy, non-replacement therapy, and other therapies that include antifibrinolytics and topical agents.

Keywords:- VWD(von Wille brand disease), VWF (von Wille brand factor), clotting factor

I. Introduction

In von Willie brand disease when a blood vessel is injured and starts bleeding, due to this condition platelets together with some clotting factors form a plug at the region of injury. therefore, the blood vessel stops bleeding. The plasma protein helps the platelets to stick together and form a clump it is called as the von Willebrand factor (VWF). It also carries factor VIII. In this type of disease condition, the ability of the blood to clot decreases leading to solid and continuous bleeding after an injury which is called von Willebrand disorder or disease (VWD). This may cause internal organ damage and rarely may lead to death.[1] Von Willebrand's disease is an autosomal inherited congenital bleeding disorder in which a deficiency of von Willebrand's factor exists. Von Willebrand's factor (VWF) is important to the process of hemostasis. First, VWF plays a role as a bridge between platelets and damage sites in the blood vessel walls, and it plays a critical role in platelet adhesion. VWF protects Factor VIII, another important player in the intrinsic pathway of the coagulation cascade, from rapid proteolytic degradation.[2] Bleeding disorders are broadly classified into primary homeostatic defects (congenital and acquired vascular abnormalities, quantitative and qualitative platelet defects, and von Willebrand disease VWD and secondary hemostatic defects (congenital and acquired coagulation factor deficiencies). The most common congenital bleeding disorder is VWD, which is due to an abnormality of VWF.[3] VWD is known for several decades, but its evidence-based criteria are not available for the diagnosis of the most frequent phenotype called type 1. This type 1 phenotype represents overall 80–90% cases are registered at specialized centers with a reported incidence in the

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general population of up to 1% in the worldwide population.[4] Type 1 VWD is caused by a quantitative deficiency of the von Willebrand factor (VWF) . In type 1 VWD, all the multimeric forms of Von Willi brand Factor are present in a reduced concentration and there is a decrease of VWF antigen (VWF: Ag) and VWF ristocetin cofactor activity (VWF: RCo). In, type 2 VWD is described by a qualitative or quantitative defect of the VWF molecule, displayed by a inequality reduced VWF:RCo/Ag ratio, often followed by an abnormal multimeric form, or by a reduced affinity of the VWF molecule with FVIII. Genetic transmission is generally co-dominant or dominant. In exceptional cases, VWD is transmitted in a degenerating manner with an almost complete VWF deficiency in homozygote patients, this type of phenotype is called type 3 and it is easily diagnosed.[3] The molecular justification for the diagnosis of type 1 vWD is mostly undefined. The laboratory based determination of vWD and its various variants are made up on the basis of therapeutical and functional studies of the vWF, and studies the factor VIII levels, and specialized electrophoretic analyses (multimer gels) method utilized for diagnosis. The main concentration of therapy or treatment for most patients with vWD is desmopressin, a pharmacologic agent that stimulation and release of endogenous pools of vWF. Cryoprecipitate and selected factor VIII concentrates are useful sources of external vWF for the treatment of patients does not show response against the drug desmopressin.

Table 1.1: List of Factors Involve In the blood Clotting

Factor	Name	Function
I	Fibrinogen	Clot formation
II	Prothrombin	Activation of I, V, VII, VIII, XI, and XII, Platelets
III	Tissue factor	Initiation of thrombin formation from the zymogen prothrombin.
IV	Calcium	Seals the blood clots by altered the structure of fibrin.
V	Proaccelerin	Important role to control step in the clotting process.
VI	Accelerin	Activation of prothrombin to thrombin.
VII	Proconvertin, stable factor	Responsible for fibrin deposition & platelet activation
VIII	Antihemophilic factor A	Also called von Willi brand factor, and also help to platelets stick together, like glue to form a clot at the site of injury and stop the bleeding.
IX	Christmas factor or Anti haemophilic factor B	Help the blood form clots to stop bleeding
X	Stuart-Prower factor	Used to treat or prevent bleeding in people with hereditary factor X deficiency.
XI	Plasma thromboplastin antecedent	Forms blood clots in response to injury.
XII	Hageman factor	Essential for surface activated blood coagulation tests.
XIII	Fibrin stabilizing factor	Stabilizing the formation of a blood clot.

History: The initial description of vWD dates back to the observation of Dr. Erik von Willebrand in the 1920s of an extended family, many of whose members suffered from severe and sometimes fatal hemorrhagic complications.[5] It is named after the Finnish doctor, Erik von Willebrand (1870-1949). He was the first person to describe the hereditary bleeding disorder in the families in Aland Islands. He could not identify the actual cause of the disorder but was able to distinguish it from hemophilia and other bleeding disorders. [6]The disorder described by von Willebrand was distinguished from classical hemophilia by an autosomal mode of inheritance, the predominance of mucocutaneous bleeding, and a prolonged bleeding time (BT). Descriptions of patients with similar clinical features also appeared in the American medical literature around the same time.[5]Von Willebrand disease (VWD) has been recognized as a heterogeneous disorder since its first description by

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Erik Adolf von Willebrand in 1926.[7] von Willebrand's disease (vWD) is a hemorrhagic disorder first described in 1926 by the Finnish physician Erik von Willebrand who found it in patients on one of the Aland islands in the Gulf of Bothnia.[8] The disease was characterized by nose bleeds, bleeding after tooth extractions, bleeding from the female genital tract, and wounds. He found the bleeding time to be prolonged despite a normal platelet count. In 1956 and 1957, Nilsson et al. [9,10] Nilsson described 13 Swedish patients with an inherited autosomal dominant bleeding disorder characterized by an antihemophilic factor (AHF, FVIII deficiency, and prolonged bleeding time.[11]

Classification of Von Willebrand disease

VWD is classified into three major types, I, II, and III, according to the quantity, structure, and function of the patient's vWD. It is of two forms one is the Inherited form and another acquired form. The international society of Thrombosis and Homeostasis has classified vWD based on the qualitative and quantitative defects and nature of the von Willi brand factor. [12] According to this classification, type 2 vWD is again classified into four different types type 2A, type 2B, type 2M, and type 2N.[13] It is an inherited disease and 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 of the parents type 3 is inherited only if the gene is passed from both parents[1]. Acquired VWD is seen in patients with autoantibodies.[12]

Type I:- VWD type I, with an autosomal dominant mode of inheritance, is the most common form, accounting for about 70'% of all affected families.[14] All the vWF multimers are present in plasma but in reduced amounts. In type IB, which is much less common than type IA, all multimers are also present, though the large multimers are more reduced in quantity than the small multimers [15] Type I is a quantitative or qualitative defect but the clotting impairment may not be seen clear. Genetically changes in the VWF are common in life threatening cases and milder in cases of type 1 VWD [16]. Person with type 1 VWD lead a normal life and they have low levels of VWF. These low levels of VWF have been decrease due to mutations that shows the effect of gene expression. The intracellular transportation of VWF sub-units is impaired leading to life threatening, and dominantly inherited type 1 VWD.[17,18] Type 1 VWD can also be caused by the rapid clearance of VWF from the plasma of affected person. These result leads to decreases the cleavage time of circulating vWF multimer by ADAMTS-13. As a result, the clearance shifts multimer distribution in plasma towards those that are initially secreted by the endothelial cells.[19,20]There is a normal distribution of the high molecular weight multimers. Laboratory findings reveal that the ratio of the activity of VWF and its antigen is proportionately decreased.[21] The type 1 variant accounts for over 80% of patients with vWD and in all likelihood results from a variety of genetic defects. It is characterized by modest quantitative defects and mild clinical symptoms. The inheritance of a single null allele has been associated with type 1 vWD in some pedigrees, although many individuals who are obligate carriers of such alleles are found to be normal in every respect.[22,23]

Type II : In this Type 2 cases of these type of condition are more difficult to diagnose due to the qualitative or quantitative nature of the defect. These types of defects range from the non-appearance of certain protein multimers for binding during hemostasis to unacceptable binding. This Type 2 sub-group accounts for approximately 20-30% of cases.[24] Qualitative variants include types 2A, B, N, and M, and included within this broad category are variants defined under the original classification scheme. The molecular basis of type 2 variants has been intensely studied, providing clear information on the deleterious nature of mutations.[25] The mode of inheritance is autosomal dominant, except for a few cases where it is recessive. Several mutations have been identified, most of them cluster within a segment in the A2 domain coding for a site in the normal vWF that is sensitive to proteolysis in vivo. Increased sensibility to proteolytic degradation may be one mechanism responsible for the deficiency of the largest multimers.[26]

(a)Type 2A vWD : Under conditions of high shear stress, vWF is uniquely able to support the adhesion of platelets to exposed subendothelial proteins, a function that requires the presence of large vWF multimers composed of covalently linked subunits. The initial step of this process is the formation of dimers through disulfide bond formation in the C terminus of the pro-vWF subunit (Figure 1). The creation of larger multimers, which range in size up to 100 subunits, from pro-vWF dimers begins in the trans-Golgi and is completed in secretory vesicles. The propeptide plays a critical role in this process, serving both to properly align the amino termini and

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to catalyze disulfide bond formation.[27,28] The reduction of high molecular weight multimers in subtype IIA is caused either by their impaired intracellular transport (group 1 mutations[29]) or their enhanced proteolysis by the vWF-specific protease (group 2 mutations[30]). The first mutations were reported in 1989.[31] The various mutations causing this subtype are located in the A2 domain of VWF or affect cysteine residues C1272 and C1458 respectively in the A1 domain; they are listed in the vWF mutation database.[32]

(b)Type 2B vWD : It is characterized by a decreased level of large multimers in the plasma and a markedly increased proteolysis.[33,34] Like in type 2A, the proportion of ristocetin co-factor activity is lower[35].Even in type 2B but the proteolytic activity does not affect the multimerization in the Golgi apparatus. The mutations that cause the type 2B vWD and do not impair. These small multimers do not make a rapid effective platelet adherence and inhibiting the direct interaction of platelets with connective tissue.[36] Type 2B vWD must be differentiate from a platelet-type vWD, which is similar in presentation. Patients in the latter group have a primary platelet defect that results from mutations in the platelet vWF receptor (GPIb-IX).[37]

(c)Type 2M vWD : In this variant, includes patients with decreased VWF platelet-dependent functional parameters in the presence of high molecular weight multimers independent of further issues of differentiation, such as an abnormal structure of individual multimers or supranormal multimers as seen in subtype vWD type 2M Vicenza. Most of the mutations detected to date are clustered in the A1 domain of vWF.[32,38] Subtype VWD 2M Vicenza in several families is associated with a mutation in the D3 domain of VWF.[39] The problem in diagnosing vWD type 2M is similar to the situation in type 1 disease since the quality of the multimer analysis leaves some range of interpretation. In fact, mutations in the A1 domain in patients previously misdiagnosed or misinterpreted as having vWD type 1 (or type 2M) were found on reappraisal to correlate with a relative decrease of high molecular weight multimers, suggesting that the correct classification was vWD type 2A.[40]

(d)Type 2N vWD : In this, variants of von Willie brand disease decline in the binding affinity for factor VIII. In some cases, both the alleles of VWF may have factor VIII binding mutations. But in most of the cases of type 2N, only one of the two alleles has the mutation while the other may express a little or no mutation.[41] In type 2N, the level of factor VIII is lower when compared to the VWF Antigen. This led to misdiagnosis as hemophilia A. The patients should have clinical symptoms of hemophilia A.[42,43,44]

Type III

It is caused by a recessive mutation that leads to an undetectable VWF level. Hence it is called as a severe form.[41] The mutations that commonly cause type 3 VWD are non-synonymous substitution and nonsense mutations.[45] It is characterized by serious mucosal bleeding with no distinguishable VWF antigen.[42] In type 3 vWD, vWF is undetectable and FVIII levels are generally less than 10 U/dl. It is estimated that the incidence of type 3 vWD is approximately 1–2 per million population, although regional differences are known to exist.[46,47]

Symptoms of vWD : The symptoms of von Willebrand's disease vary from each patients, depend upon the level of von Willebrand factor in the blood and other symptoms depend upon the age, and sex. In case of children the von Willebrand's disease, is the most frequent presenting signs are bruising and epistaxis.[48] In case of adults, the most common signs are hematomas, menorrhagia, and bleeding from minor lesion. The large number of patients (60 to 80%) have bleeding after operation or tooth extractions shows the occurrence of self-reported bleeding symptoms derived from the large Von Wille brand disease at the Netherlands (WiN) study[49]; similar prevalences have been reported in other studies.[50] A well-known, serious, and possibly life-threatening bleeding complication is gastrointestinal bleeding from angiodysplasia.[51] It is most common in elderly patients with type 2 or 3 von Willebrand's disease.[49,51] Intraarticular bleeding(joint bleeding) is a frequent complication in patients with hemophilia(factor VIII deficiency) but has not been announced as a big problem in patients with von Willebrand's disease, it may be a presenting symptom in those with type 2N (type 2 subtype Normandy) or type 3 disease. It is now known that joint bleeding occurs in a considerable number of severely affected patients, potentially leading to arthropathy and reduced joint function.[52]The U.S. Centers for Disease Control and Prevention (CDC) surveyed 75 women with VWD enrolled in United States hemophilia treatment centers and found that their most common bleeding symptoms were bruising; nosebleeds; bleeding after injury,

Table 1.2 : Signs and symptoms of vWD

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surgery, or tooth extraction; postpartum bleeding; and the most common bleeding symptom of all, menorrhagia.[53] Overall, a high prevalence of menorrhagia has been reported among women with VWD, with a range of 32% to 100%.[54,55] Not only is there a high prevalence of menorrhagia among women with VWD, but there is a high prevalence of VWD among women with menorrhagia; the prevalence of VWD from published studies of menorrhagia is between 5% and 20%.[56-57] Menorrhagia is defined as heavy menstrual bleeding that lasts for more than 7 days or results in the loss of more than 80 mL of blood per menstrual cycle.[58] There are problems with this definition of menorrhagia. One problem is the stringency of the definition. Another is the impracticability of measuring menstrual blood loss. The practitioner, therefore, must rely on a menstrual history and clinical impression. A recent study attempted to assess the volume of blood loss by means of specific clinical features. In plan of action regression model, the variables that prediction of menstruation blood dropping of more than 80 mL were clotted bigger than a 50-pence in size, low ferritin, and changing a pad or tampon more than hourly.[59] With the help of these type of symptoms the practitioner easily detect which have menorrhagia.

Mouth bleeding	Nose bleeding	A heavy or prolonged period
Bleeding	Irregular uterine bleeding	Bleeding in the joint or muscles
Blood in urine	Tendency to bleed easily	Bleeding gums
Easy bruising	Excessive bleeding during childbirth	Heavy bleeding after a tooth removal or a surgery

Diagnosis of vWD : History is very important in consideration of an initial workup. Many assays or examination have been represented. In general cases, many recommend that an initial examination include the following are CBC (complete blood count), PT (Prothrombin Time), PTT(Partial Thromboplastin Time), INR(International normalised Ratio), platelet function assay (PFA-100), blood type, bleeding time, and VWF assays or examination. The specific VWF assays involve the evaluation of Factor VIII, VWF, and Ristocetin cofactor activity. These tests allow for the initial evaluation of potential quantitative or qualitative defects that may be present. However, there are limitations to certain tests. First of all, not all the diagnoses tests are routinely available in all laboratories. Further, many of these assays are affected by hormones, stress, chronic disease states, pregnancy, and even blood type. Therefore, if one set of tests seems to rule out the condition, but symptoms are still present, it is worthwhile rechecking the assays and consulting with a hematologist.[60] Type 1 and type 2 disease type of patients do not have large bleeding problems. Hence, early diagnosis of this disease is difficult. Otherwise, early diagnose of disease is easy to identify in type 3 people as they have severe bleeding problems.[1]

Bleeding history: It can be considered to be the patient has three different hemorrhagic symptoms or when the bleeding score is more than 3 (males) or 5 (females).[61-62] Scoring systems and the importance of examine the bleeding history and the chance of having VWD (especially type 1) outside the defined population.[61-63]

Total blood count: In this diagnosis test it includes evaluating the hemoglobin, hematocrit, platelet count (PC) and morphology, prothrombin time (PT), activated partial thromboplastin time (aPTT). Thrombin time can be measured optionally.[64] Usually, individuals or patients with VWD have a normal thrombin time, prothrombin time, platelet count and fibrinogen or thrombin level. Some individuals have a prolonged a PTT which is consistent with VWD whereas, it may be normal in mild or moderate cases.[65-66] Depends upon the type and severity of the disease, the level of hemoglobin and hematocrit range goes downward from normal .[67]

Platelet count and prothrombin time: In most of single patients with Von Wille brand disease, the platelet count is as usual whereas it is decreased in type 2 VWD patients.[2]With the use of PFA-100, platelet counts yield a low closure time (CT). closing hour time is the time taken by the platelets to clog a hole impregnated with hydrolysed collagen

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or epinephrine. With this type of test, one can evaluate the platelet adhesion or aggregation.[68] The majority of the single patients with VWD other than type 2N have abnormal PFA-100(Platelet function analyzer) results. It is use for screening the general populations for VWD has not yet been well-established.[69,70,71]Patients with severe type 1 and type 3 VWD show abnormal PFA-100 conclusion. Whereas in , mild to moderate type 1 VWD patients and some type 2 cases do not show unusual outcome or conclusion.[72-73] The patient with VWD have a normal prothrombin time.[35]

Activated partial thromboplastin time: The activated partial thromboplastin time is usually normal. It may be extended in case of decreased levels of FVIII. In type 1 VWD, the FVIII levels in plasma are higher than the normal range of factor VIII. In type 2 disease individuals or patients and other than type 2N, the FVIII levels are 2-3 times higher than VWF. However, it is lower in type 2N Patients. In type 3 individuals, the plasma levels of FVIII are below 10 IU/dl.[74,75]The normal FVIII concentration of plasma is 50-150 IU/dl approx.[35]

VWF: Ag (VWF antigen): In this diagnostic test, the plasma concentration of VWF is measure by using methods like Enzyme linked immunosorbent assay (ELISA). Results should be either as IU/dl or IU/ml.[1] The normal dose range of VWF: Ag is 50-200 IU/dl.[35]In type 1, 2A, and 2B patients, the levels are decreased. In type 2N VWD, VWF:Ag levels are normal level.[61]

VWF: RCo (ristocetin cofactor activity assay): It is a functional assay in which the ability of VWF to agglutinate with normal platelets is measured. The interaction between the Von Willi brand factor and the normal platelets is initiated by an antibiotic, ristocetin. The use of ristocetin antibiotics in clinical trials has been stopped because it causes thrombocytopenia. But in laboratory tests, it is quite used because it is the most widely accepted functional test for the Von Willi brand factor.[64] The normal dose range is 50-200 IU/dl.[35] The degree of VWF is low in type 1, 2A, and 2B VWD and is found to be normal in the case of type 2N patients. They may be very in type 2M patients.[2]

ABO blood group: Several studies have been conducted to know the influence of the ABO blood group on plasma levels of VWF.[76-77] It was found that 66% of the variation in the plasma levels of VWF was determined genetically in 30% of the genetic component was explained by the ABO blood group.[78] Patients in the O group have the lowest VWF levels as compared to the AB group Patients who have the highest levels. The importance of these blood groups on the plasma levels of VWF makes it difficult to diagnose type 1 VWD since the normal range of VWF: Ag in O group individuals is below 50 IU/dl, which is generally considered as the lower normal limit.[79] The VWF: RCo level in individuals with the O blood group is significantly lower than those in the non-O group.[80]

RIPA (ristocetin-induced platelet aggregation): It is mainly used to diagnose type 2B VWD.[35,64] It is generally done using low-concentration ristocetin (usually mutations in the platelet VWF receptor. The word is termed plate-type vWD or pseudo vWD and it can be separated from type 2B by VWF: PB (VWF: platelet binding) assay. In patients with type 3 VWD, RIPA (Ristocetin-induced platelet aggregation)will be decreased at higher concentrations of ristocetin. This test is not sensitive to diagnosing other types of VWD.[64]

Genetic tests: Mutation analysis is used in identifying mutations in the VWF gene associated with types 2A, 2B, 2M, 2N, and some other forms of type 1 and 3 VWD. It is useful in differentiating mild hemophilia A from type 2N. In the condition of Mild hemophilia, it has no VWF mutations and follows X-linked inheritance; whereas type 2N is due to VWF mutations and follows autosomal recessive heritage. It is also used to differentiate type 2B from type 2M; type 2A from 2B.[81-82] Mutation analysis also helps in managing future pregnancies by determining the causative mutation in families with type 3 VWD.[2] This analysis is less useful in diagnosing type 1 VWD which has a complex and variable genetic basis.[83] Most of the mutations in type 2B, 2M, and 2N VWD cluster in cDNA which directs the synthesis of specific regions of VWF.[84] Mutations cluster in the A2 domain in common forms of type 2A VWD during the time they may be scattered throughout the gene in less common forms of type 2A.[64]

Treatment of vWD : Von Willebrand's disease is a heritage bleeding disorder with an incidence as high as 1 to 2 percent in the general population, according to screening studies. In contrast, estimates based on referrals for symptoms of bleeding suggest a prevalence of 30 to 100 cases per million, which is similar to the prevalence of hemophilia A.[4-85] There are certain standard recommendations to guide therapy for VWD.[86-87] The mainstay of VWD treatment is the replacement of the deficient protein (VWF)Von Wille brand factor.[88] The different therapies used in treating VWD are Non-

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replacement therapy, replacement therapy, and other therapies.[89]

Non-replacement therapy, DDAVP (1-des amino-8- D-arginine vasopressin):

Desmopressin is a synthetic derivative of the antidiuretic, vasopressin. It is chemically known as 1-des amino-8-D-arginine vasopressin. Through its agonist effect on vasopressin V2 receptors, it stimulates the release of VWF from endothelial cells.[90-91] DDAVP increases the plasma concentration of VWF through cyclic AMP-mediated release of VWF from endothelial cell Weibel-Palade bodies.[92] Factor VIII levels are also increased but its storage and release mechanisms have not yet been elucidated fully.[94-95] Though DDAVP (Desmopressin acetate) produce the release of tissue plasminogen activator (tPA), it is rapidly indolent by plasminogen activator inhibitor (PAI-1) and then fibrinolysis or bleeding does not appear to be promoted after treatment by DDAVP.[96] It can be given intravenously or intranasally or can also be administered subcutaneously if available.[89] Indicated for most of the type 1 patients, and some type 2A patients.[1] The standard dosing of DDAVP is 0.3 mg/kg intravenously in 30-50 ml of normal saline over 30 min.[91-96] Subcutaneous doses are identical to i.v. dose. Nasal instillation contains 150 µg per metered nasal puff (0.1 ml of a 1.5 mg/ml solution). The dose is one puff for those whose body weight is 50 kg weight.[89] It is not indicated for type 2B VWD as there was a fall in the platelet count after its use.[97] It is not clinical use in type 3 VWD because there is no clinically relevant rise in FVIII or VWF: RCo activities.[98] Common side effects include hyper or hypotension, migraine or gastrointestinal upset, and facial flushing.[88,91]

Replacement therapy: Humate-P and Alphanate SD/HT are plasma-derived concentrates to replace VWF.[88] These products should not be exchanged with one another as they are not identical and differ in the ratios of FVIII to VWF.[99-100] Humate-P is administered I/V and it is contraindicated for patients who cannot tolerate desmopressin or patients who required long time treatment. It can also be used in any variant of type 2 disease and severe type 3 cases.[1] When fix up at the recommended volume, each milliliter of the product contains 50-100 IU/ml VWF: RCo and 20-40 IU/ml FVIII activity.[101] Alphanate SD/HT, upon regeneration to the recommended volume, each milliliter of the product contains 40-180 IU/ml FVIII activity and not less than 16 IU/ml VWF: RCo activity.[88] Adverse reactions include urticaria, chest tightness, rash, pruritus, and edema.[102]

Other therapies, antifibrinolytics:

Aminocaproic acid and tranexamic acid are the antifibrinolytics used in VWD therapy. These therapies are act by inhibiting the conversion of plasminogen to plasmin and as a result inhibit fibrinolysis. Therefore, to stable(balance) the clots which are formed.[103] These drugs can be given orally or intravenously to give the treatment of mild mucocutaneous bleeding in patients with VWD. The adult dose of aminocaproic acid is 4-5 gm as a loading dose given orally or I/V 1 h before invasive protocols. It is then followed by 1 g/h given orally or I/V or 4-6 g for every 4-6 h orally until bleeding is inhibited for 5-7 days post-operatively[88]. The total daily dose should not increase 24 g/24 h to minimize potential side effects. Children require weight-based dosing which can also be used in adults (50-60 mg/kg).[88,104] Tranexamic acid is given intravenously at a dose of 10 mg/kg every 8 hours.[88] Both drugs cause nausea, vomiting, and rarely thrombotic complications.[100]

Topical agents: Topical bovine thrombin (Thrombin-JMI) is used as a topical agent in the case of less amount of bleeding from the capillaries and small vein. Fibrin sealant is another topical agent which is used in certain surgical conditions, but it is ineffective to treat heavy arterial bleeding. It gives good results when used as an adjunct to hemostasis in dental surgery in individuals with VWD.[105-106] Topical collagen sponges are also used in controlling bleeding wounds.[107]

II. Conclusion:

In the past 15 to 20 years, there have been major advances in our understanding of the pathophysiology, molecular basis, and management of von Willebrand's disease. The important choices which are available to the treatment (desmopressin and plasma concentrates) which are effective to control the bleeding in most affected patients with this disease. Even though virus-inactivated products appear to have enough safety, it is hoped that the von Willebrand factor that is composed by recombinant DNA techniques undergo clinical trials and become available for replacement therapy. In the genetic testing for the management of families with genetically bleeding disorders including VWD, there is an evolution in this direction. Testing centers and counsellors play an important role to support patients. For all scientific development in clinical research in bleeding disorders, then there is

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a requirement for experienced clinicians and laboratory scientists with experience (skills) in hemostasis. Training opportunities have to be developed for hemostasis specialists.

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