International Journal of Pharmaceutical research and Applications
Volume 9, Issue 1, Jan.-Feb. 2024, pp:1646-1651 www.ijprajournal.com ISSN: 2456-4494

A Review on Von Willebrand's Disease

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Date of Submission: 08-02-2024 Date of acceptance: 23-02-2024

ABSTRACT

Most commonly acquired dying clutter, to begin with depicted in Aland Islands by Erik von Willebrand. It happens as a result of diminish in plasma levels or imperfection in von Willebrand figure which may be a huge multimeric glycoprotein. Monomers of this glycoprotein experience N-glycosylation to make dimers which get organized to give multimers. Official with plasma proteins (particularly calculate VIII) is the most work of von Willebrand calculate. The illness is of two shapes: Acquired and procured shapes. Acquired shapes 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 predominant than all other types. Mucocutaneous dying is gentle in type 1 while it is gentle to direct in type 2A, 2B, and 2M. Sort 2N has comparative indications of Haemophilia. The pathophysiology of each sort depends on the subjective or quantitative surrenders in von Willebrand figure. The conclusion is based on von Willebrand calculate antigen, von Willebrand factor action test, FVIII coagulant movement and a few other extra tests. Comes about ought to be analysed inside the setting of blood bunch. von Willebrand figure multimer examination is fundamental for writing and sub writing the illness. The administration of the malady includes substitution treatment, non-replacement treatment and other treatments that incorporate antifibrinolytics and topical agents.

KEY WORDS: VWD, VWF, AVWD, FVIII, VWF: PB, VWF:GB, FVIII:C

I. INTRODUCTION

Von Willebrand illness, acquired blood clutter characterized by a delayed dying time and an insufficiency of figure VIII, an imperative blood-clotting specialist. Von Willebrand infection is caused by lacks in von Willebrand calculate (vWF), an atom that encourages platelet attachment and may be a plasma carrier for calculate VIII.There are a few diverse shapes of von Willebrand infection. Type 1 is the foremost common and mildest frame of the illness. Type 2 is subdivided into four extra subtypes of changing seriousness. Types 1 and 2 are acquired as autosomal overwhelming characteristics. Type 3, the foremost serious shape, is passive and requires that the characteristic be acquired from both guardians. Von Willebrand malady may too be obtained (procured von Willebrand disorder), with signs and side effects showing up in adulthood; the obtained frame, which tends to happen in conjunction with resistant clutters, isn't caused by an acquired deformity. [1-2]

EPIDEMOLOGY

Estimation of the prevalence of VWD (overall or by specific type) were available from 22 of the 168 sources and varied according to the method of estimation. Multinational estimates for VWD (all types) were reported from two global sources, and a cross-sectional study conducted in Western Europe and Israel. Based on expert opinion, Orphanet reported that globally 0.6–1.3% of the general population was affected by VWD (unspecified data source and time period), and that the prevalence of symptomatic VWD was approximately 10 per 100,000.9 The 2019 annual global survey of the World Federation of haemophilia yielded a referral-based estimate of 1.5 per 100,000 based on the number of patients (with all types of VWD) registered in haemophilia treatment centers.10 The European cross-sectional study yielded a population-based estimate of 0.05 per 100,000 for type 3 VWD.[3]

ETIOLOGY

Within the majority of cases, VWD is an acquired condition. The VWF quality is found close the tip of the brief arm of chromosome 12. The quality is composed of 52 exons and ranges a add up to of 180kb of the human genome; hence, it is comparable in estimate to the FVIII quality.

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Expression of the VWF quality is confined to megakaryocytes, endothelial cells, and, conceivably, placental syncytiotrophoblasts. A functional, nonfunctional duplication (pseudogene) is show on chromosome 22.VWF exists as an arrangement of multimers shifting in atomic weight between 0.5-kd (dimer) and 20 million Kd (multimer). The building squares of multimers are dimers, which are held together by disulfide bonds found close the C-terminal conclusion of each subunit.[4]

VON WILLERBRAND'S FACTOR

It could be a blood glycoprotein that advances haemostasis, particularly, platelet attachment. It is insufficient and flawed in von Willebrand illness and is included in numerous other maladies, counting thrombotic thrombocytopenia purpura, Heyde's disorder, and conceivably haemolytic-uremic syndrome. Expanded plasma levels in numerous cardiovascular, neoplastic, metabolic (e.g. diabetes), and connective tissue diseases are presumed to arise from adverse changes to the endothelium, and may predict an increased risk of thrombosis. [5-6]

VWD type I

VWD type I causes a mild to moderate quantitative deficiency of vWF (i.e. about 20-50% of normal levels). In individuals with vWF levels<0.3IU/ml, type I is usually inherited in autosomal dominant fashion, in those with levels>0.3 IU/ML, mutations show variable penetrance

VWD type II

VWD type II is due to the subjective von Willebrand's factor variations from the norm and is subdivided into type IIA, IIB, IIN, and IIM. VWD type IIA is the foremost common subjective variation from the norm of VWF and it is related with particular misfortune of huge and medium sized multimers. In most of the cases have autosomal overwhelming legacy. VWD type IIB characterized by the misfortune of the expansive of multimers happens through a component unmistakable from the type IIA. Perceptions to date have distinguished a basic region of VWF included within the distinguished single amino corrosive substitutions is thought to result in a pick up of work, driving to unconstrained official of VWF to platelets

VWD TYPE III

Patients with VWD type III, is an extreme, quantitative lack of relation with exceptionally a small or no recognizable plasma or platelet VWF, have a significant dying clutter. VWD type III shows up to result from the legacy of a mutant VWF quantity from both guardians. Within the most clear demonstrate, VWD type I would basically organize to the heterozygous frame of VWD type III. In any case of legacy demonstrate more prominent complexity. VWD typeIII is much rarer than the anticipated reccurance of 1 case per 40,000 people. In spite of the fact that few transformations have been recognized in families with immaculate VWD type I, a few VWD type I cases have been proposed to be due to a mutant VWF subunit that meddling in a prevailing, negative way with the typical allele, book keeping for the autosomal prevailing legacy [7-9]

ACQUIRED VWD

Procured VWD may be an uncommon clutter that comes about from the improvement of antibodies to VWF, or from intemperate cleavage of VWF multimers due to conditions that

TYPE	DEFECT	INHERITANCE	CLINICAL MANIFESTATIONS
Type 1 (Accounts for~3/4 of cases)	Quantitively defect (i.e. not enough VWF)	Autosomal dominant	Bleeding: none- severe
Type 2 (Type 2A, 2B,2M,2N)	Qualitative defect (i.e. dysfunctional vWF)	Autosomal dominant (common), Autosomal recessive(uncommon)	Bleeding: moderate - severe
Type 3 (Accounts for <5% of cases)	Profound quantitative defect (i.e. a total or near total absence of vWF	Autosomal recessive	Bleeding: severe (Clinically similar to hemophila A)

create tall shear stretch within the circulatory system. Obtained VWD may emerge in assortment of settings including lymphoproliferative, cardiovascular, and myeloproliferative infections

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and regulatory settle with treatment of the cause.[10]

SYMPTOMS

The most common symptoms of von Willebrand disease in decreasing frequency include 10

1.Heavy or prolonged menstrual bleeding (menorrhagia)
2. Frequent and easy bruising (Trauma)
3. Bleeding in the throat and mouth
4. Frequent or hard to stop nosebleeds
5. prolonged gum bleeding after a dental procedure
6. Heavy or extended bleeding after surgery

Other symptoms (more common in type 3 VWD) include:

Blood in the stool (haematochezia) due to bleeding in the stomach or intestine

Blood in urine (haematuria) due to bleeding within the kidneys or bladder

Severe joint pain or swelling (hemarthrosis) due to bleeding into the joint space [11]

DIAGNOSIS:

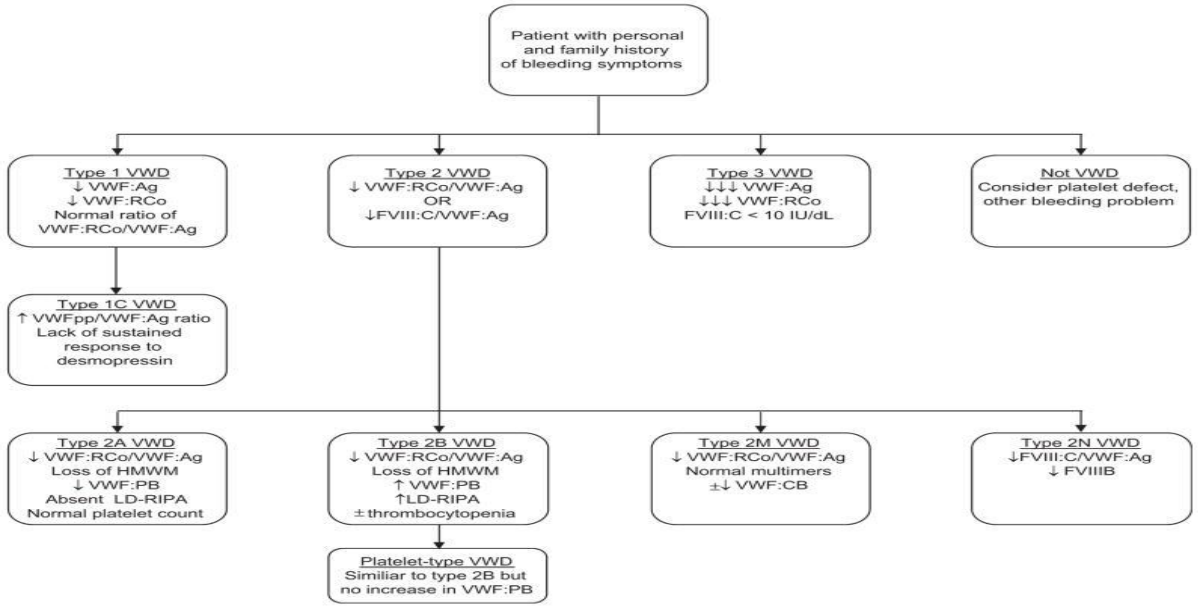
VWD may be caused by either a quantitative or a qualitative defect of vWF. Initial evaluation for VWD requires a combination of screening tests, as no single test can confirm the presence of fully functional vWF. Along with assessment of vWF protein presence, routine screening tests include the assessment of vWF -platelet and vwf-fviii interactions.

Laboratory testing for VWD

VWD screening tests	
VWF: Ag	↓ in type 1, ↓ most type 2, undetectable in type 3
VWF: RCo	↓in type 1, ↓↓most type 2, undetectable in type 3
FVIII:C	↓or normal in type 1, most type 2, ↓↓ in type 2N, type 3
VWF: RCo/VWF:Ag ratio:	↓in type 2A, 2B, 2M
VWD Confirmatory Tests	
VWF Multimer distribution:	Abnormal in type 2A and 2B
VWF:GB	Abnormal in type 2A and 2B, some type 2M
VWF: PB	Increased in type 2B
LD-RIPA	Increased in type 2B and platelet-type VWD
VWF-FVIIIB	Decreased in type 2N
VWFpp	↑VWFpp/VWF:Ag ratio in type 1C
VWF gene sequencing	Most helpful in type 2 variants

VWF: Ag = vWF antigen, VWF: RCo = VWF ristocetin cofactor activity; FVIII:C = factor 8 activity; VWF: CB = VWF collagen binding; VWF: PB = platelet binding; LD-RIPA = low- dose ristocetin-induced platelet aggregation; VWFpp = VWF propeptide; ↓ = mildly decreased; ↓↓= moderately decreased; ↓↓↓= greatly decreased. [12-13]

DIAGNOSIS ALGORITHM:[14]



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TREATMENT;

Once the diagnosis results are obtained, then the treatment approach has two main components: patient education and selection of the appropriate therapy. Physician must instruct patients to avoid medications with antiplatelet activity by checking the ingredients in the prescription and over-the-counter preparations for acetylsalicylic acid-containing medications. It is essential that patients understand the importance of coordinating the medical management of bleeding episodes and the implementation of prophylaxis before surgical procedures.[15]

LIST OF MEDICATION THAT HAS ANTIPLATELET EFFECTS:

Antiplatelet agent: Acetylsalicylic acid, NSAIDS
Antimicrobial agents: High dose penicillin's, cephalosporins, nitrofurantoin
Cardiovascular medications: propranolol, furosemide, quinidine
Others: Antihistamines, caffeine, valproate, heparin, ethanol

The choice of treatment for patients with VWD depends on the clinical severity, the type of VWD and the risk of bleeding. The three main therapeutic modalities used in the treatment of VWD are desmopressin acetate (DDAVP), transfusion with plasma concentrates that contain VWF and antifibrinolytics agents

DESMOPRESSIN ACETATE: DDAVP (1-desamino-8-D-arginine vasopressin)

Desmopressin is a synthetic derivative of the antidiuretic, vasopressin. It is chemically known as 1-desamino-8-D-arginine vasopressin. In 1997, mannucci et al (10) first described use of DDAVP to control bleeding in patients with VWD. DDAVP has been used in VWD patients with mild to moderate bleeding problems and for prophylaxis of patients undergoing surgical procedures. The mechanism by which DDAVP aids haemostasis is by increasing plasma levels of factor VIII:C and VWF through their release from endothelial storage sites. Following intravenous administration of DDAVP at a dose of 0.3µg/kg, plasma levels of FVIII:C transiently increase 3-6-fold above the basal levels, the bleeding time shortens, and the plasma FVIII:C and VWF levels increase within 15to 30 min, peak within the first hour, then decline over 4to 8 h DDAVP is also effective when administered subcutaneously. A concentrated intranasal spray preparation of desmopressin acetate is effective equally in patients with type 1VWD and permits the home treatment of mild bleeding episodes.

The side effects of DDAVP are usually mild or benign and include facial flushing, headache, mild tachycardia, nausea and abdominal cramps. Water retention, hyponatremia and seizures have been reported in young children and infants who received multiple doses of DDAVP and aggressive hydration. DDAVP is contraindicated in patients with type 2B, 3VWD. Type 2B patients may develop in vivo platelet aggregates and thrombocytopenia. type 3 patients are usually unresponsive to DDAVP

PLASMA CONCENTRATES:

Humate-P and Allophanate SD/HT are the plasma derived concentrates to replace VWF. These products should not have been interchanged with one another as they are not identical and differ in the ratios of FVIII to VWF. Humante-P is administered intravenously and is indicated for the patients who cannot tolerate desmopressin or patients who require prolonged treatment. It can also be used in any variant types of disease and severe type-3 cases. When reconstituted at the recommended volume each millilter of the product contains 50-100 IU/ml VWF: RCo and 20-40 IU/ml FVIII activity. Each milliliter of alphanate SD/HT upon reconstitution 40-180 IU/ml FVIII activity and not less than 16IU/ml VWF: RCo activity. Adverse reactions include urticaria, chest tightness, rash, pruritus and oedema.

ANTIFIBRINOLYTICS:

For bleeding or surgery in the oral cavity, an antifibrinolytic agent should be used. Tranexamic acid is an antifibrinolytic agent that can be use along with DDAVP or factor concentrates for dental surgery or mouth bleeding events. A dose of 25 mg/kg orally, every 8 h for 10 days is required to prevent fibrinolysis and allow wound healing. A 5% solution of tranexamic acid mouthwash made from IV preparations can effectively prevent local bleeding in minor oral cavity bleeding

Aminocaproic acid is another antifibrinolytic agent used currently. The dose is 50 to 100 mg/kg every 4 to 6 hr for 7 to 10 days (max dose 24 g/24 hr). Generally, antifibrinolytic agents are not recommended for internal haemorrhages [16-17]

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II. CONCLUSION

VWD is an inherited bleeding disorder caused by the abnormalities of VWF (von Willebrand's factor). There are changes evaluated in the direction of genetic testing for managing of families with hereditary bleeding disorders includes VWD. Testing centres and physicians, counsellors play vital role. It is imperative that family doctors and paediatricians become familiar with the treatments for VWD and the interpretation of the laboratory results. Training opportunities and skilled clinicians have to be developed for haemostasis specialists. Most importantly patients need to be educated about the disease to coordinate treatment and prevent complications.

Conflict of interest: nil

Acknowledgment: The authors thank the curious personalities who had provided necessary facilities to the work.

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