Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology 28 (2016) 442–445

Contents lists available at ScienceDirect

Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology

journal homepage: www.elsevier.com/locate/jomsmp

Oral Medicine/Review article

A medical elaboration on von Willebrand disease with its dental management

M. Aparna*,[1]

Department of Oral Medicine and Radiology, Government Dental College, Kozhikode, Dental College Building, Dental College Road, Medical College Campus, Kozhikode, Kerala 673008, India

ARTICLE INFO

Article history:
Received 14 January 2016
Received in revised form 15 May 2016
Accepted 16 June 2016
Available online 16 July 2016

Keywords:
von Willebrand disease
Bleeding disorder
Dental management

ABSTRACT

Objective: von Willebrand disease (vWD) is the most common type of autosomally inherited bleeding disorder representing a range of quantitative and qualitative pathologies of the adhesive glycoprotein, von Willebrand factor (vWF). Since symptoms are often mild, a significant majority of patients remain undiagnosed.
Method: A review from the literature which imparts the knowledge on background, pathophysiology, classification, diagnostic measures and treatment modalities of this fatal bleeding disorder.
Results: With all forms of vWD, however, bleeding episodes can be severe and may require treatment.
Conclusions: A primary care physician should play a role in recognizing the signs and symptoms of vWD and in referring patients for proper management. The treatment of bleeding in vWD involves the use of desmopressin and plasma-derived vWF concentrates and a variety of adjunctive agents.

Contents

1. Background

In 1926, Finnish hematologist, Erik A. von Willebrand, described the first patient with the bleeding disorder that now bears his name. On graduating from the University of Helsinki, he moved to the Aland Islands, a dependency of Finland, in the Gulf of Bothnia. There he concentrated his studies on a familial bleeding disorder with normal platelet counts, called 'Alandic Hemorrhagic Disease'. The patient was severely affected with multiple episodes of mucosal

☆ Asian AOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

* Tel.: +91 7559801262.
E-mail address: appu.rags@gmail.com
[1] Permanent address: Padmasree House, Kottooli Post, Kozhikode 673016, Kerala, India.

http://dx.doi.org/10.1016/j.ajoms.2016.06.005
2212-5558/

bleeding that led to her death at the age of 13. Four of her eleven siblings were also severely affected. With the recognized autosomal inheritance pattern in his study of other family members, von Willebrand named the disorder 'Hereditary Pseudohemophilia' [1]. This newly discovered malady, unlike hemophilia, affected both sexes. It became known as von Willebrand disease (vWD), which is the most common genetic coagulation disorder affecting 1–2% of the population worldwide. Gingival bleeding and epistaxis are frequently encountered in the affected individuals [2].

2. The von Willebrand factor (vWF) gene and protein

The 175-kb vWF gene is located on the short arm of chromosome 12 and comprises 52 exons. The vWF gene sequence is replicated in part by a partial vWF pseudogene on chromosome 22. This evolutionary remnant recapitulates exons 23–34 of the vWF gene with 3% variance, a fact that significantly complicates the genetic analysis of this central region of the vWF gene. The 9-kb vWF transcript encodes a pre-pro-vWF protein of 2813 amino acids. The protein undergoes extensive posttranslational modifications, including the removal of leader and propeptide sequences, dimer and eventual multimer generation, and the addition of many N-linked and O-linked carbohydrate structures. A recently revised annotation of the vWF protein structure indicates that whereas the platelet- and collagen-binding A domains of the protein form globular-like structures, a series of repetitive vWC domains toward the C-terminus provide the protein with increased length and flexibility, thus facilitating the transition between compact and extended conformations under conditions of shear stress in the vasculature [3].

vWD is a result of either quantitative or qualitative defects in the vWF. The vWF is produced in the endothelial cells and bone marrow megakaryocytes and consists of multimers that are stored in platelet alpha granules and in Weibel–Palade bodies of endothelial cells. The vWF plays a crucial role in both primary and secondary hemostasis. In primary hemostasis, vWF facilitates platelet adhesion to sites of vascular injury by binding to platelets at the glycoprotein Ib (GPIb) receptor. To achieve secondary hemostasis, vWF binds and stabilizes factor VIII (FVIII), thus preventing its circulatory clearance and reabsorption [4–6].

3. Classification and pathophysiology (Table 1) [7,8]

3.1. Diagnosis

Diagnosis depends on the demonstration of an abnormality in one or more of the following tests: vWF activity, vWF antigen (vWF: Ag), FVIII activity, bleeding time and optionally vWF multimers and ristocetin induced platelet aggregation (RIPA) [9].

vWF activity is also known as ristocetin cofactor activity (vWF: RCo). Ristocetin is an antibiotic derived from the Actinomycete Nocardia lurida. It binds both vWF and platelet GPIb causing agglutination of formalinized platelets, which can be quantified and compared to a standard curve to obtain ristocetin cofactor activity. Plasma vWF antigen is measured by ELISA or latex bead assay. FVIII activity can be detected by one stage coagulation assay using FVIII deficient plasma. Bleeding time becomes helpful if it comes abnormal. vWF multimers are measured using electrophoresis. RIPA measures affinity of vWF to GPIb by limiting [ristocetin]. It is used to diagnose Type IIB variant [9].

Table 1
vWD is classified on the basis of criteria developed by the vWF Subcommittee of the ISTH, first published in 1994 and revised in 2006.

vWD type	Pathophysiology
Type I	Partial quantitative vWF defect. All multimers are present
Type IIA	Qualitative defect. ↓ platelet-dependent vWF function. Loss of HMWM
Type IIB	"Gain of function" defect, ↑ vWF binding to platelet GPIb, ↑ clearance of the complex, loss of HMWM, ↓ platelet numbers
Type IIM	↓ vWF dependent platelet adhesion. No HMWM loss
Type IIN	↓↓ vWF affinity for FVIII. No HMWM loss
Type III	Complete quantitative defect of vWF

Classification based on pathophysiology.
Abbreviations: vWF, von Willebrand factor; HMWM, high molecular weight multimers; GPIb, glycoprotein Ib; ↓ = decreased; ↑ = increased.

3.2. Acquired von Willebrand syndrome (AVWS)

AVWS refers to defects in vWF concentration, structure or function that are not inherited directly but are consequences of other medical disorders. Laboratory findings in AVWS are similar to those in vWD and may include decreased values for vWF: Ag, vWF: RCo or FVIII. AVWS usually is caused by one of three mechanisms: autoimmune clearance or inhibition of vWF, increased shear-induced proteolysis of vWF, or increased binding of vWF to platelets or other cell surfaces [10,11].

4. Discussion

Contrary to other rare diseases, over the last few decades vWD has benefited from a greater understanding of the causes and mechanisms responsible for its development as well as of the molecular and physiological characteristics of the disease and its proper diagnostic and clinical management. This has undoubtedly aided in the design of highly appropriate treatment schedules. Therapies to prevent or control bleeding in persons with vWD follow three general strategies. The first strategy is to increase the plasma concentration of vWF by releasing endogenous vWF stores through stimulation of endothelial cells with desmopressin. The second approach is to replace vWF by using human plasma-derived, viral-inactivated concentrates. The third strategy uses agents that promote hemostasis and wound healing but do not substantially alter the plasma concentration of vWF. The three treatment options are not mutually exclusive, and patients may receive any one or all three classes of agents at the same time. The appropriateness of therapeutic choice depends on the type and severity of vWD, the severity of the hemostatic challenge, and the nature of the actual or potential bleeding [12].

4.1. Non-replacement therapy with desmopressin to elevate vWF

Desmopressin (DDAVP) is a synthetic derivative of the antidiuretic hormone, vasopressin. The mechanism by which desmopressin increases plasma concentration of vWF is through cyclic adenosine monophosphate (cAMP)-mediated release of vWF from endothelial cell Weibel–Palade bodies [13]. The mechanism for the rise in FVIII was thought to be due to its consequent stabilization in plasma FVIII levels [14]. Nasal administration of high-dose desmopressin acetate (Stimate) (150 μg per single spray) is often effective for minor bleeding, but i.v. administration (0.3 $\mu g\,kg^{-1}$ over 20 min) is the preferred route for prophylaxis of surgical bleeding and for treatment of major hemorrhage. Desmopressin can also be administered subcutaneously (0.3 $\mu g\,kg^{-1}$) [15–17].

4.2. Therapies to elevate vWF: replacement therapy

Replacement therapy aims at correcting vWF deficiency, allowing platelet adhesion and aggregation, and increasing potentially low FVIII concentrate (FVIII: C) level. They are lyophilized concentrate of purified vWF and FVIII contains other plasma proteins including fibrinogen and albumin. The concentrates thought to be most useful for the management of vWD unresponsive to DDAVP