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CASE REPORT

von Willebrand Disease in Dental Clinic: An Exclusive Case Report with Review of Literature

M Aparna

ABSTRACT

von Willebrand disease (vWD) is the most common type of autosomally inherited bleeding disorder affecting up to 1% of the world's population. The disease represents 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. In the hemostasis laboratory, the measurement of vWF antigen and ristocetin cofactor activity is key components in the diagnostic algorithm for vWD. With all forms of vWD, however, bleeding episodes can be severe and may require treatment, particularly during or following surgery or dental work. The primary care physician can and 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. This article gives a detailed description of the case report on a 5-year-old boy who presented with vWD in dental clinic and also imparts the knowledge on back ground, pathophysiology, classification, diagnostic measures and treatment modalities of this fatal bleeding disorder from dental perspective.

Keywords: Bleeding disorder, Dental perspective, von Willebrand disease.

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INTRODUCTION

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 bleeding that led to her death at the age of 13. Four of her 11 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 to 2% of the population worldwide. Gingival bleeding and epistaxis are frequently encountered in the affected individuals.[2]

Senior Lecturer

Department of Oral Medicine and Radiology, KMCT Dental College, Kozhikode, Kerala, India

Corresponding Author: M Aparna, Senior Lecturer, Department of Oral Medicine and Radiology, KMCT Dental College, Kozhikode Kerala, India, Phone: 7559801262, e-mail: appu.rags@gmail.com

VON WILLEBRAND FACTOR GENE AND PROTEIN

The 175-kb von Willebrand factor (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 to 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 post-translational 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]

von Willebrand desease 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]

CLASSIFICATION AND PATHOPHYSIOLOGY (Table 1)[7,8]

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]

von Willebrand factor 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. von Willebrand factor multimers are measured using electrophoresis. Ristocetin-induced platelet aggregation measures affinity of vWF to GPIb by limiting [ristocetin]. It is used to diagnose type IIB variant.[9]

ACQUIRED VON WILLEBRAND SYNDROME

Acquired von Willebrand syndrome (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. Acquired von Willebrand syndrome 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]

Table 1: von Willebrand disease 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 vWF: von Willebrand factor; HMWM: High molecular weight multimers; GPIb: Glycoprotein Ib; ↓: Decreased; ↑: Increased

CASE REPORT

A 5-year-old male patient, reported to the dental OPD with a chief complaint of bleeding from gums since 4 days. His history (in his mother's words) included bleeding that occurred from gums spontaneously after taking food, presence of clot in mouth, easy bruising tendencies which was managed symptomatically. History of similar incidents also reported. There was no history of pain, pressure sensation, paresthesia, difficulty in eating, swallowing, increased or decreased salivation, pus discharge, trauma or infection. This was his first dental visit. His medical history revealed that he was a known case of vWD. In his first visit (8 months old) to the physician, the investigations carried out revealed; bleeding time 22 minutes 30 seconds, clotting time 7 minutes, platelets count 2.8 lacks/mm^3 and C-reactive protein positive (1.2 mg/dl). In his second visit (10 months old) to the physician, the investigations carried out revealed; bleeding time 15 min, prothrombin time 13.9 seconds, activated partial thromboplastin time 76.7 seconds, thrombin time 16.8 seconds, FXIII and clot retraction normal, platelet count 3,67,000/mm^3, direct smear showed adequate platelets of normal morphology in clumps, and vWF assay 9.8% (47–197). His family history revealed his younger brother (1 year old) suffered from the same disease. His parents had non-consanguineous marriage. Birth history was uneventful. Personal history revealed that he attained milestones at appropriate age, immunization was up to date. He was predominantly a nonvegetarian, with no deleterious habits and used to brush his teeth once daily with tooth brush and paste in horizontal direction.

On general physical examination, he was conscious and cooperative, moderately built and nourished, well oriented with time, place and person. All vital signs were within the normal limits. Height of 96 cm and weight of 13 kg were recorded. There were no signs of pallor, icterus, cyanosis, clubbing, lymphadenopathy and edema. On extraoral examination, he had mesocephalic head, straight profile and competent lips. His eyes, ears, nose, temporomandibular joint (TMJ), skin over the face, hair and regional lymphnodes showed no abnormalities. On intraoral soft tissue examination, labial mucosa, buccal mucosa, vestibular area, frenal attachment, retromolar area, tonsils, hard palate, soft palate and tongue revealed no abnormalities, except bleeding from gingiva. On intraoral hard tissue examination, there was dental caries in relation to (irt) 54, 55, 64, 75, 84, 85 (Figs 1 and 2). There was mild amount of stains and deposits. The oral hygiene index according to Green and Vermillion was found to be good.

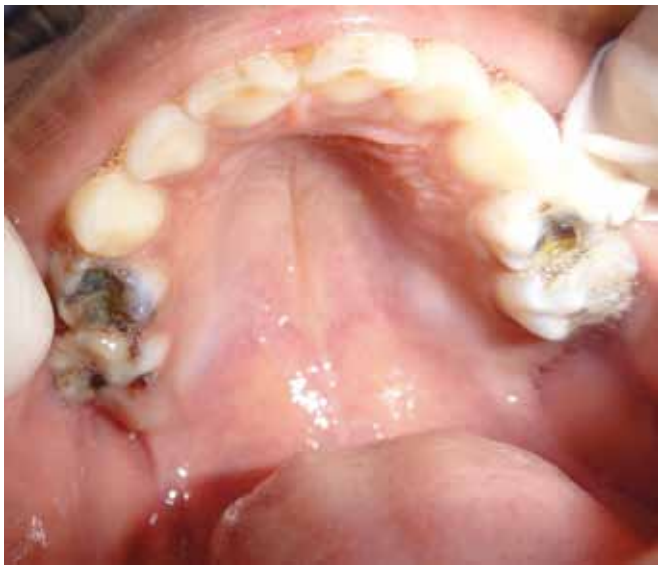

Fig. 1: Dental caries in relation to 54, 55 and 64

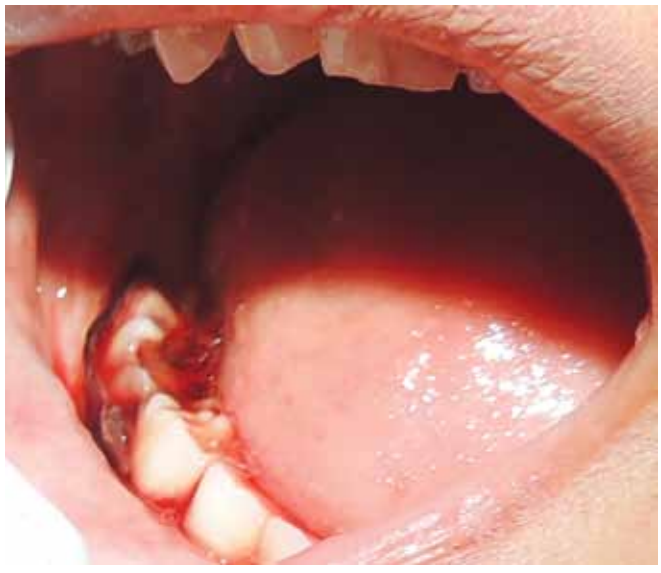

Fig. 2: Blood clots on the right vestibular region and occlusal aspect of decayed 84, 85; bleeding gingiva with respect to 84, 85 regions

On local examination of the lesion, intraoral soft-tissue inspection revealed, bleeding from gingival region and blood clots in mouth irt 75, 84, 85 regions (Fig. 2). Patient spited clot from mouth frequently. Intraoral hard tissue inspection revealed, dental caries involving enamel, dentin and pulp irt 64, 75 and dental caries involving enamel and dentin irt 54, 55, 84, 85. On palpation, blood clots can be removed using a probe from teeth. Teeth were tender. Hence based on the history given by the patient's guardian and clinical examination carried out, a provisional diagnosis of von Willebrand disease with bleeding, chronic pulpitis irt 64, 65, 75, 85 and dental caries irt 54, 55, 84 was given. Further investigations were carried out on admission to rule out other clotting disorders (Table 2). Based on the reported history, clinical and laboratory findings a final diagnosis of vWD with intraoral bleeding was made. Treatment planned in this case included management of bleeding and restoration of decayed teeth. Treatment rendered was, patient referred to the department of pediatrics for the management of the bleeding which included: frozen fresh plasma transfusion-1 pint 150 ml @ 7.5 ml/hr over 2 hours, injection and Lasix 15 mg IV stat mid transfusion. Follow-up was done after 2 weeks of episode. Patient did not show any signs or symptoms of bleeding (Figs 3 and 4). Patient kept on regular follow-ups and medicated for tablet tranexa 500 mg (1/2 tid) (100 mg/kg/dose) in similar incidents.

Table 2: Laboratory investigations carried out in patient

Erythrocyte sedimentation rate	*20 mm/1hr*
Prothrombin time	15.2 sec (prolonged)
Activated partial thromboplastin time	75.4 sec (prolonged)
vWF Ag	15 IU/dl (low)
vWF-RCo	14 IU/l
Factor VIII	26 IU/dl (low)
Bleeding time	15 mins (prolonged)
Clotting time	9 mins
Complete blood count (CBC)	
Hemoglobin	11. 5 gm/dl (low)
Total count	10.8 × 10^3/µl
Differential leukocyte count	
Neutrophil	30%
Lymphocyte	60%
Eosinophil	6%
Monocyte	4%
Basophil	0%
Platelet count	273 ×10^3/µl
RBC count	4.34 million/mm^3
PCV	34.8%
MCV	80.2 fl
MCH	26.5 pg
MCHC	33 gm/dl

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

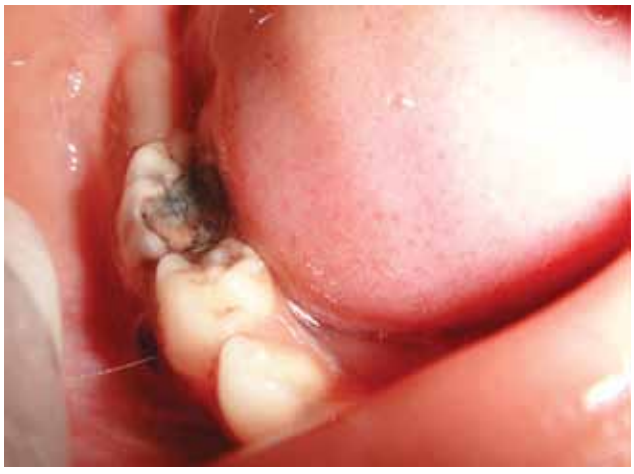

Fig. 3: Right vestibular region and occlusal aspect of decayed 84, 85 after the management of von Willebrand bleeding

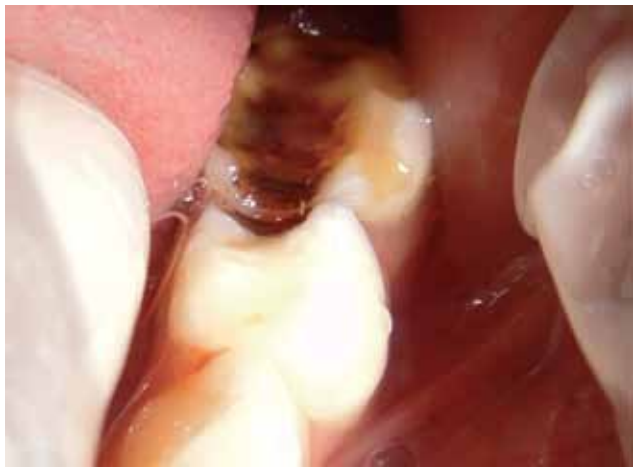

Fig. 4: Decayed 75 with no blood clots after the management of von Willebrand bleeding

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]

Nonreplacement 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 iv administration (0.3 µg kg^{-1} over 20 mins) is the preferred route for prophylaxis of surgical bleeding and for treatment of major hemorrhage. Desmopressin can also be administered subcutaneously (0.3 µg kg^{-1}).[15-17]

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 were BPL 8Y, Haemate-P (2.5 IU vWF:RCo for each unit of (FVIII:C), Alphanate (0.6 IU vWF:RCo for each unit of FVIII:C), VHP-vWF concentrate and cryoprecipitate.[18-20]

OTHER THERAPIES FOR vWD

Antifibrinolytics

The antifibrinolytic drugs aminocaproic acid and tranexamic acid are agents that inhibit the conversion of plasminogen to plasmin, inhibiting fibrinolysis and thereby helping to stabilize clots that have formed. The drugs can be used orally or iv to treat mild mucocutaneous bleeding in patients with vWD.[21] In patients with mild-to-moderate vWD, tranexamic acid given topically in the oral cavity (swish and swallow or spit) every 6 hours has been used for prophylaxis in dental surgery, in combination with applied pressure, other topical agents and suturing of surgical sites.[22]

Topical Agents

Topical bovine thrombin is an aid to hemostasis for topical therapy of accessible minor bleeding from capillaries and small venules. Fibrin sealant [Tisseel VH (Baxter)], consisting of human thrombin, fibrinogen concentrate and bovine aprotinin] is indicated as an adjunct to hemostasis in certain surgical situations, but it is not effective for the treatment of massive and brisk arterial bleeding. Fibrin sealants have been used with good results as adjunctive therapy for dental surgery in persons with hemophilia or vWD. Topical collagen sponges are also approved for control of bleeding wounds.[22-24]

Advanced Therapies

In the future, the different types of advanced therapies, such as gene therapy, cell therapy and tissue engineering as well as the more recently developed induced pluripotent stem cells (iPSC) technology, may offer innumerable clinical applications for the treatment of vWD. Gene therapy consists of transplantation of genetically modified cells so that they may produce a functional protein, and cell therapy in the transplantation of living

cells into an organism in order to repair tissue or restore a deficient function.[25]

DENTAL MANAGEMENT OF PATIENTS WITH vWD

Persons who do not have a definite diagnosis of vWD but who have vWF:RCo levels of 30-50 IU dL^{-1} and have a bleeding phenotype may merit treatment or prophylaxis of bleeding in certain clinical situations (grade B, level III).[12] Individuals who are more than 2 years old, have vWD, and have not already been vaccinated should be immunized against hepatitis A and B (grade C, level IV).[26] Persons with vWD should be counseled to avoid aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), and other platelet inhibiting drugs (grade C, level IV).[27] Epistaxis and oropharyngeal, soft tissue, or minor bleeding should be treated with intravenous or nasal desmopressin. For prophylaxis for minor surgery, initial treatment should be expected to achieve VWF: RCo and FVIII activity levels of at least 30 IU dL^{-1} and preferably higher than 50 IU dL^{-1} and should be maintained for 1 to 5 days (grade B, level III). For persons with vWD, management of minor bleeding (e.g. epistaxis, simple dental extraction or menorrhagia) with desmopressin and proper fluid restriction can be performed without laboratory monitoring unless desmopressin is used more than three times within 72 hours (grade C, level IV).[28] For persons with mild to moderate vWD, antifibrinolytics combined with desmopressin are generally effective for oral surgery. von Willebrand factor concentrate should be available for persons who cannot receive desmopressin or who bleed excessively despite this combined therapy (grade B, level IIb).[29] Topical agents, such as fibrin sealant or bovine thrombin, may be useful adjuncts for oral surgery in persons with vWD. Careful attention to hemostasis of an extraction socket and to suturing of sockets is also important in oral surgery in persons with vWD (grade C, level IV).[22] For fillings done under infiltration with local anesthetic, treatment with DDAVP or concentrates is not needed. Treatment should be given if an inferior dental block is to be used (grade C, level IV).[28] In responsive patients a single dose of DDAVP given with tranexamic acid is usually sufficient to cover dental extractions. Treatment should be monitored at least with a FVIII:C assay unless DDAVP has been shown to be effective on previous occasions. If DDAVP cannot be used a single dose of a vWF containing concentrate can be used aiming to achieve 50 IU dL^{-1} VWF:RCo. Tranexamic acid should be given orally (starting before treatment) and/or as a mouthwash for 5 days afterwards.[30]

CONCLUSION

Understanding the underlying pathophysiology of vWD, its subtypes, and diagnostic tests is important. Collaboration with a hematologist is crucial. History of excessive bleeding, especially after tooth extraction, should be given its due attention. The course of treatment would depend on the type of vWD defect and the extent of surgery. To maintain primary hemostasis, the presence of functional vWF and platelets is necessary, whereas in secondary hemostasis FVIII is required to participate in the intrinsic clotting pathway. Finally, 'although optimism is clearly justified in patients with vWD, fantasy is best avoided in order to not raise false expectations in the patients suffering from this rare disease that may be subject to either curative or palliative treatment'.

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