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Case Report

Dental Management of Patient With Von Willebrand Disease

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Abstract

Von Willebrand disease is a lifelong bleeding disorder in which your blood doesn't clot well. Some people may suspect they have a bleeding disorder when they have heavy bleeding after a dental procedure. Mutations in the von Willebrand disease gene cause von Willebrand disease. The von Willebrand factor as a blood clotting protein was provided by the VWF gene and is essential for the formation of blood clots.

Methods: Ten year old boy come with his mother to the Department for preventive and pediatric dentistry, University Dental Clinic Centar St Pantelejmon- Skopje. During a visit to the pediatric dental clinic, the need for extraction of several primary teeth was detected with a clinical and rtg examination. The child has already made blood test and results showed a borderline of vWF Ris Co and vWF Ag and hypoagreligidity of the Tr. Timely boy complains of chest pain and also has a chronic eczema. The child is monitored in a hematologic ambulance due to the vWF Ag boundary level and hypoaggregability of Tr. For haemostasis after the extraction of a primary tooth, local application of amp.Tranexamic acid and fibrin foam is recommended by his heamatologist.

Conclusion: For successful extraction of the primary teeth in patient with von Willebrand disease consultation with a haematologist is necessary.

Keywords: Von Willebrand disease; Dental care; Oral health

1. Introduction

Children with haematological diseases are a very important group of a dental aspect, because they are relatively often encountered in dental clinics. This particularly applies to children with haemorrhagic syndrome, who in the clinical picture have either spontaneous bleeding or bleeding after injury. Children with haemorrhagic syndrome require dentists more care than other patients because they are constantly exposed to the risk of bleeding during dental intervention. Haemorrhagic diseases are manifested by petechiae, ecchymoses, hematomas, haemarthrosis, epistaxis, haematuria and others. Many diseases in children with haemorrhagic syndrome are often manifested with characteristic changes in the mouth. This means that the dentist is the one who often first notices these changes and is therefore obliged to refer the patient to a hematologist. Of great importance for the early diagnosis and proper treatment of these diseases is the role of dentist , because the dentist may be the first one who suspect or recognize one of these diseases. It is very important to diagnose a haemorrhagic disease in the early childhood because the proper diagnosis means to provide timely preparation and to avoid the danger of the child's health and life.

Von Willebrand's disease (Vascular haemophilia) is a hereditary disease that is transmitted by an autosomal dominant gene, but also some time by an autosomal recesive gene. Women are more likely to get sick. The patients have lack of Von Willebrand's coagulation factor, which is found in plasma, platelets, megakaryocytes, and endothelial cells [1]. Von Willebrand Factor (vWF) is a large glycoprotein with a broad range of physiological and pathological functions in health and disease [2].

Von Willebrand disease is a lifelong bleeding disorder in which your blood doesn't clot well. Some people may suspect they have a bleeding disorder when they have heavy bleeding after a dental procedure. Mutations in the von Willebrand disease gene cause von Willebrand disease. The von Willebrand factor as a blood clotting protein was provided by the VWF gene and is essential for the formation of blood clots. In fact 95-97% of all coagulation deficiencies belong to the three group of disease: Von Willebrand disease, Hemophilia A and Hemophilia B [3].

The pathogenesis of the disease is not sufficiently clear, but it has been established that quantitative and qualitative disorders of the VIII factor which is involved in the process of blood coagulation (deficiency of the factors which affect the time of coagulation and those required for platelet adhesion and aggregation) are established. In children with vascular haemophilia, major irregularities of blood vessels can be detected [1]. The first suspect of some people with Von Willebrand disease occur when they have a bleeding disorder and they have heavy bleeding after a dental procedure or, for women, during a menstrual period.

Clinical disease is characterized by a tendency of bleeding in the early period of childhood, which manifests itself with bleeding from the skin (bruising with minimal trauma), mucous membrane of the oral cavity (gingiva), nose and mucous membrane of the digestive organs. Prolonged haemorrhage occurs in children after traumatic injuries,

and it must be taken into consideration that these children must be prepared by the haematologist before any oral surgical intervention was undergo [1].

Three types of inherited VWD exist and one type of the disorder that isn't hereditary. Type 1 is the most common form of inherited VWD. About 60% to 80% of people with VWD have this type and they don't have enough von Willebrand factor in their blood. Patients with Type 1 VWD have 20% to 50% of normal levels of the VWFactor. Symptoms of Type 1 VWD are mild. Type 2 is the second most common form of inherited VWD. It's caused by patient own VWD factor which do not work well. From all patients with VWD, 15% to 30% of them have chance to have Type 2 of VWD. Symptoms of VWD Type 2 range from mild to moderate. Von Willebrand disease Type 3 is the rarest form of inherited VWD and is found in 5% to 10% of cases. Patient with this type, typically have no von Willenbrand factor and also have very low levels of another protein needed for clotting. Type 3 has the most severe symptoms. Acquired form of VWD is possible to appear if patients have an autoimmune disease, like lupus. An autoimmune disease occure when patients body's natural defense system (immune system) fights itself. Patients can also get acquired VWD after taking certain medications, or from heart disease or some types of cancer [2-5].

The patients with type 1 and type 2 of the VWD have symptoms that range from mild to moderate. They include: frequent large bruises from minor injuries, frequent or hard-to-stop nose bleeds, Blood in your stool or pee (from internal bleeding), heavy bleeding after a cut, accident, or minor medical procedure, bleeding for a long period of time after major surgery and heavy or long menstrual periods. Patients with Type 3 VWD, may have all the symptoms of Type 1 and Type 2, plus episodes of severe bleeding for no reason. They also might experience severe pain and swelling in their soft tissues and joints because of bleeding. Most people with Von Willebrand disease can't be cured, but with good management treatment and self-care and control, most people with this disease can have active lives. Von Wilebrand disease as a hematologic disorder is the most frequently inheried bleeding disorder, described as a deficiency of von Willebrand factor and affect 0.8-2% of the general population in Europe and Amerca [6-8]. Thus, this study aimed was to show one case report of patient with von Willebrand disease and to overview all oral health aspects of patients with von Willebrand disease.

2. Case Report

Boy was ten year old when with his mother come to the Department for preventive and pediatric dentistry, University Dental Clinic Centar- Skopje. During a visit to the dental clinic, the need for extraction of several primary teeth was detected with a clinical examination and a rtg examination. The child has a borderline of vWF Ris Co and vWF Ag and hypoagreligidity of the Tr. Timely complains of chest pain and also has a chronic eczema. The child is monitored in a hematologic ambulance due to the vWF Ag boundary level and hypoaggregability of Tr. For haemostasis after the extraction of a primary tooth, local application of amp. Tranexamic acid and fibrin foam is recommended. After the consultation with the pediatric haematologist we star with the extraction of the primary teeth. Even though there was a need for extraction of more primary teeth, we began to extract each tooth individually.

The mother provides us with the anamnesis' data that her child previously have convulsions on two occasions. In February 2018, myringotomy procedure and adenoidectomy were made to the child, and there was no prolonged bleeding. Also an appendectomy has been made to a child four years ago. The mother denies familial history of hemorrhagic diathesis. Clinical examination of the child shows squamous scalp and initial alopecia hot spots, erythema-squamous lesions of the corpse and limbs. Consultation with a dermatologist is required.

The child was received at the Otorhinolaryngology Clinic due to frequent suppurative otitis, decreased hearing and snoring during sleeping.With the general endotracheal anesthesiaIn OETA transmeatally mirrinotomy bilaterally was done, during which plentiful serous secretion right and mucosal secretion on the left was aspirated. The ventilation tubes (Grommet-Shepard) [9] were placed and sol.Citeral. together with exact haemostasis was conducted. Then, with adenoma, excessive adenoid lymphatic tissue was removed from the epipharynx. Exact haemostasis was conducted during the intervention. Hygiene-dietary diet and rest for up to 14 days after the intervention was recommended by otolaryngology. The finding of the otomicroscopic examination was unequivocal. Audiometric testing which was done six months after the placement of "gromets" bill shows a moderate mixed hearing loss on both ears. The patient was send to oto-microscopic examination. Subspecialist audiologist prescribed sprey Fixonase 2X1 during the day in the nose and also chymoral tablets 3X1. Our patient belongs to type 2 Von Willebrand disease. From the blood test table 1 the boundary level of Von Willebrand Factor Ris Co activity [%] 51 and Von Willebrand Factor vWF Ag [%] 48 was observed.

Analysis	**Description of the status / laboratory service**	**Normal**	**Results**
Test on the haemostatic system			
	platelet count	150-450	**193**
	Hematocrit	35-50	**41,2**
	Prothrombin time	9,8 (13) 14,2	**11**
	Activated partially	27,9(33) 37,7	**30**
	Thrombin time	16,1(22) 24,1	**17**
Quantitative determination of coagulation factors			
	Antihemophilic globulin	50-150	**112**
	Chrismas factor(F IX)	50-150	**92**
	Von Willebrand Factor Ris Co activity [%]	50-150	**51**
	Von Willebrand Factor vWF Ag [%]	50-150	**48**
Aggregation and monitoring of antiaggregatory therapy			
	ADP optical [%]	69-88	**14**
	Colagen optical [%]	70-94	**67**
	Ristocetin optical [%]	87-102	**73**
Blood test-white blood cells			

	WBC [10exp9/L]	3,5-10	**7,2**
	LYM [10exp9/L]	0,5-5	**1.8**
	MID [10exp9/L]	0,1-1,5	**0.5**
	GRAN [10exp9/L]	1,2-8	**4,9**
	LYM% [%]	15-50	**25,6**
	MID% [%]	2-15	**6**
	GRA% [%]	35-80	**68.4**
Blood test-red blood cells			
	RBC [10exp12/L]	3,8-5,8	**5.44**
	HGB[g/L]	110-165	**139**
	MCV[fl]	80-97	**75.8**
	MCH[pg]	26,5-33,5	**25.6**
	MCHC [g/L]	315-350	**337**
	RDW% [%]	10-15	**14.3**
	RDWa [fl]	30-150	**50.9**
Blood test-blood plates			
	MPV[fl]	6,5-11	**8.5**
	PCT[%]	0,01-9,99	**0.16**
	PDW[fl]	0,1-99,9	**12.1**
	LPCR[%]	0,1-99,9	**17.9**

Table 1: Blood analysis.

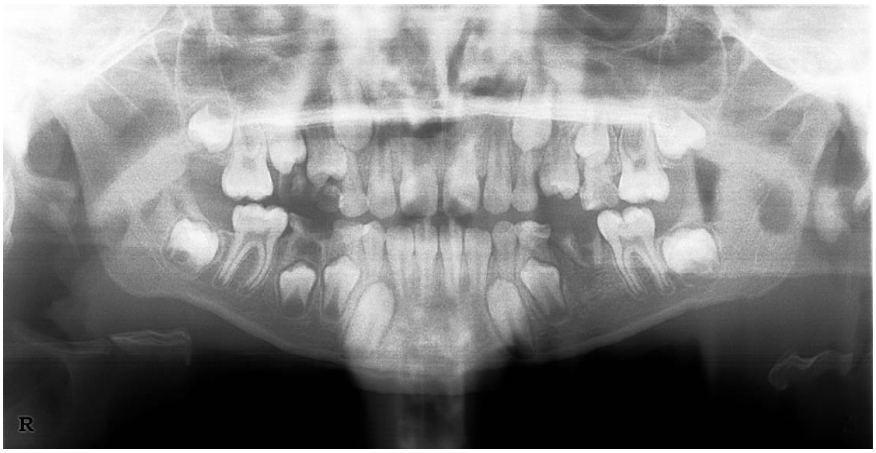

Figure 1: Orthopantomogram before the start of the primary teeth extraction.

3. Discussion

This disorder is characterized by a mutation of the von Willebrand factor itself or in the quantity of the creation of the von Willebrand factor. This factor is responsible for primary haemostasis by helping platelet aggregation and adherence to the endothelial lining and acting as a carrier factor for factor VIII. Factor VIII has a significantly shortened half-life when it is not bound to Von Willebrand factor; this is the reason that factor VIII levels in laboratory analysis have increased. There are three subtypes of hereditary Von Willebrand disease. Types 1 and 2 are autosomal dominant, and type 1 is the most common form of the disease (approximately 70 per cent). Type 1 represents the quantitative deficiency of the von Villebrand factor itself. Symptoms range from mild or moderate to severe. Deficiency can be due to abnormally rapid clearance of the protein or inadequate production.

Type 2, which is usually autosomal dominant, is a qualitative abnormality of von Willebrand factor. Type 2 is further subdivided into four subtypes 2A, 2B, 2M and 2N. The classification is based on where the mutation occurs in the von Villebrand factor itself.

Type 2A is a qualitative defect in which the quantitative levels are normal, but the ability of the factor to bind to platelets is reduced. This type of von Willebrand factor also does not unite well with other von Willebrand factors, resulting in reduced large multimers, which in turn results in decreased platelet adhesiveness. Hence, the results of the antigen analysis of Von Willebrand factor are normal, but the values of the cofactor and large multimers are reduced or absent.

Type 2B (approximately 5 per cent) contains a platelet-binding defect site, which actually increases platelet binding for Von Willebrand factor. This removes platelets from circulation, causing thrombocytopenia. It is important to determine if the patient has this subtype, especially if therapy is proposed, because treatment with DDAVP can actually aggravate the condition. DDAVP causes an increased release of von Willebrand factor, followed by an increased platelet binding of the von Willebrand factor and the removal of even more platelets from the circulation, which exacerbates thrombocytopenia.

Type 2M is characterized by a qualitative defect and can create appropriate multimers; however, its ability to bind to platelets is reduced. Hence, the plasma antigen levels are normal, large multimers are present, but the cofactor values are reduced.

Type 2N (N is from Normandy, where this type was first described) is a rare autosomal recessive disorder. The defect affects the ability of Von Willebrand factor to bind Factor VIII, but the factor binding factor VII remains normal (as well as the amount of available von Willebrand factor), but the factor VIII levels are greatly reduced. Because this subtype is recessive, a split allele must be inherited in order for symptoms to occur. It may be difficult to distinguish this subtype from factor VIII deficiency (haemophilia), because in both conditions patients have low levels of factor VIII. Background Willebrand disease type 2N should be considered when the patient has a family

history of autosomal penetrance (present in both males and females unrelated to the sex, according to Mendel's principles of genetics, and is not related only to the X chromosome).

Type 3 is rare (approximately 1 in a million people) and is characterized by complete absence or with very low levels of von Willebrand factor; this is the result of a variety of genetic defects, including nonsense, missens, and fracture mutations. These patients have severe bleeding and may first be diagnosed with factor VIII deficiency before testing Von Willebrand factor.

Von Willebrand's disease may also occure during various illnesses, usually autoimmune conditions such as systemic lupus erythematosus. Other mechanisms reduce synthesis, proteolysis, tumor cell binding, and reduced clearance of von Willebrand factor.

The main therapy in hemophiliacs in the event of bleeding is the replacement of the lack of blood clotting factor either through blood transfusions or the administration of a purified plasma concentrate or cryoprecipitate. The advantage of giving the purified plasma concentrate is that it is more effective and easy to keep. The dosing, the frequency of giving and the duration of therapy depend on what level we want to achieve as well as the half life of the anticoagulant, as well as the localization and the severity of the bleeding (injury). Half-life duration of factor VIII is about 12 hours, and factor IX is about 24 hours.

Successful treatment for a patient with vWD undergoing implant therapy was described by Kang M and Kang P. They treated a young 21-year-old patient with vWD lost tooth and required implant therapy. The implant surgery was performed without any postoperative complications, but before the application of implant therapy if is very important to have expellant collaboration with a patient’s hematologist which administer desmopressin (DDAVP) for prophylactic purpose [10].

The excessive high shear stress in the bloodstream is generated by various cardiovascular diseases, like a several congenital structural diseases, aortic stenosis, hypertrophic obstructive cardiomyopathy (HOCM), and, as well as mechanical circulatory support systems. These conditions and pathologic situations cause excessive cleavage of VWF multimers causing a loss of HMW multimers, a hemostatic disorder similar to VWD type 2A, known as acquired von Willebrand syndrome (AVWS). Radical treatment for AVWS was to remove the pathological high shear causing acquired von Willebrand syndrome [4]. More recently, recognition of an acquired condition known as acquired von Willebrand Syndrome (AVWF) has emerged in persons with hematological, endocrine and cardiovascular diseases, disorders and conditions although the hereditary form of von Willebrand disease was first described nearly a century ago [2].

Epping L, et al. in their study evaluated whether type 2 and 3 VWD determines an increased susceptibility to gingival bleeding in response to the oral biofilm. Gingival bleeding is also a main symptom of untreated periodontal

disease and plaque-induced gingivitis. They concluded that Type 2 and 3 VWD are not associated with a more pronounced inflammatory response to the oral biofilm in terms of Gingival Bleeding Index (GBI) and bleeding on probing (BOP) [11]. In the case-control study by Weickert L, 50 patients and 40 matched controls were periodontally examined, underwent professional teeth cleaning and also answered a questionnaire. Weickert L, et al concluded that gingival bleeding in VWD patients may be caused by by gingival inflammation, but it is not a real symptom of mild type 1 VWD [12].

In a case report by Argyris PP, et al. 11-year-old Caucasian female is presented with an surgical excision of the tumor like a expansile gingival mass, which was located on the posterior maxilla The patient suffered prolonged hemorrhage, after the intervention. Results of blood tests showed decreased levels of FVIII function (C) and VWF:FVIIIB. The type 2 N VWD was confirmed as heterozygosity for the missense mutation p.Arg816 Trp, by the subsequent gene analysis [13,14]. In our case the genetic analysis was not preformed.

Treatment of Von Willebrand disease

There are five modalities for the treatment of von Willebrand's disease.

1. Desmopressin (1-desamino-8-D-arginine-vasopressin [DDAVP])
2. Refund therapy for Von Willebrand factor (with the use of cryoprecipitate)
3. Antifibrinolytic agents
4. Topical agents (thrombin or fibrin sealant)
5. Estrogen therapy in women without contraindications

DDAVP is a synthetic analogue of antidiuretic hormone, without vasopressor activity. It acts by increasing the levels of Von Willebrand factor and factor VIII, indirectly stimulating the release of von Willebrand factor from endothelial cells. DDAVP can be administered intravenously, intramuscularly or intranasally. If DDAVP have to be given intravenously or intramuscularly for acute bleeding, the dose is 0.3 μg / kg (maximum 20μg). The raising of the levels of Von Willebrand factor and factor VIII occures in 30 to 60 minutes, with a duration of approximately 6 to 12 hours. Intranasal administration has become popular in patients with less critical bleeding and as a premedication before minor surgical interventions. The usual dose is 150 μg for children under 50 kg and 300μg for larger children and adults. A control dose should be administered to monitor the effects of Von Willebrand factor. DDAVP should not be administered to patients with Von Willebrand disease type 2B because it may exacerbate the disease. Also, it is not as effective in patients with severe bleeding disorders and in those complicated 3, probably as a result of a lack of backup from the von Willebrand factor. It could be said that the replacement therapy for Von Willebrand factor is the gold standard for treatment. However, for a cryoprecipitate (containing factor VIII) to contain a sustainable Von Willebrand factor, it should not be pasteurized, but only to be screened.

If possible, this should be avoided, due to an increased risk of transmission of viruses. Most Factor VIII concentrates do not contain a sufficient Von Willebrand factor with a high molecular weight; however, Humate-P (human antihyfilitary factor / von Willebrand factor complex) and Alphanate (antihyolytic factor) do not contain sufficient amounts. These drugs can be used with cryoprecipitate in patients with Von Willebrand disease type 2B or type 3, because they could not be treated with DDAVP. In case of significant bleeding, the goal of compensation therapy is to maintain the activity of factor VIII and Von Willebrand factor between 50 and 100 per cent for a period of three to ten days.

The use of pure von Willebrand factor or von Willebrand factor/factor VIII (vWF/FVIII) concentrate is recommended by treatment guidlines in patients with type 2 or type 3 vWD undergoing surgery, in patients with type 1 vWD undergoing surgery who are unresponsive, and in patients for whom desmopressin acetate is contraindicated [15]. Nowadays there is no consensus on the dosage and optimum levels of these factors . The results from the retrospective study conducted during the period from 2003 to 2014 by Zulfikar B et al indicate that surgery can be safely performed by providing adequate and timely hemostasis during and after the procedure in patients with von Willebrand disease. They concluded that perioperative and postoperative bleeding complications are rare when patients are with more more attention monitored [15].

The biologic response to desmopressin was evalueted within77 patients with type 1 von Willebrand disease (VWD) enrolled within the Molecular and Clinical Markers for the Diagnosis and Management of type 1 VWD project by Castaman G et al. [16]. Complete response to desmopressin was defined as an increase of both ristocetin cofactor activity (VWF:RCo) and factor VIII coagulant activity (FVIII:C) to 50 IU/dL or higher and partial response as VWF:RCo or FVIII:C lower than 50 IU/dL after infusion, but at least 3-fold the basal level. It seem that association between the response to desmopressin and location of mutation exist within VWD patients.

In their study complete response was noted in 83% of patients. The presence of subtle multimeric abnormalities did not hamper potential clinically useful responses, as in typical type 1 VWD [16]. Response to desmopressin is influenced by the genotype and phenotype in type 1 Von Willebrand disease [16]. Treatment of von Willebrand disease with Humate-P® [17] . For the treatment of Von Willebrand disease also replacement therapies like Humate-P and other, contraceptives, clot-stabilizing medications like Cyklokapron, Lysteda, others and drugs applied to cuts as a fibrin sealant (Tisseel VHSD) which can be placed directly on a cut and helps curtail bleeding. People with congenital hemorrhagic diatheses constitute a very small percentage of the total population and there is a lack of studies in relation with oral health aspects in hemophilia patients. Because of that fact treatment of such patients becomes a challenge to the most of dentists, because most of them have no practical experience in dealing with von Willebrand disease and other hemorrhagic disorders [18].

Antifibrinilitic therapy with tranexamic acid (Amicar) can also be used. It prevents lysis of blood coagulants and can be particularly useful in bleeding mucous membranes. This class of drugs can be given orally or intravenously. By

oral administration, the drug must be administered three or four times within 24 hours (due to the short half-life of the drug) over a period of three to seven days. Topical agents such as Gelfoam (an absorption sponge made from gelatin) and Surgicel (oxidized regenerated cellulose) soaked in topical thrombin can be used for local haemostasis. In several studies, estrogen has been found to raise levels of Von Willebrand factor in women who consume oral contraceptives and receive hormone substitution therapy. However, no study has long considered the risk / benefit ratio of hormone replacement therapy in von Willebrand's disease.

Treatment determines the clinical findings and the extent of bleeding. There are no good laboratory analyzes that correspond to the extent of the disease. The von Willebrand factor is not a reliable marker for the degree, because this value can artificially elevate in certain physiological conditions, such as stress and pregnancy, and therefore a history of bleeding is an important indication of the extent of the disease and the determination of optimal therapy.

4. Conclusion

For successful extraction of the primary teeth in patient with von Willebrand disease consultation with a haematologist is necessary. Improvement in communication among hematologists, dental specialists who work at hospitals and those in paediatric dental practices could be very important to establish an effective dental management of patients with Von Willebrand disease. There is a lack of epidemiological studies about the oral health status of patients with Von Willebrand disease.

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