

Case Report

Von Willebrand Disease Type 3: A Case Report

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Abstract

Type 3 Von Willebrand disease (VWD) is the rare severe form of bleeding disorder due to complete absent of von willebrand factor (VWF) which is essential for the hemostasis. It is an inherited autosomal recessive trait either homozygous or heterozygous mutations of the gene that affect the clotting factors in the blood. In the present report, the researcher explains a case of 21 years old girl known case of type 3 VWD got admitted at tertiary hospital with the complaints of excessive vaginal bleeding (menorrhagia), fatigue, and tiredness for the last 3 months. She was first diagnosed type 3 von willebrand disease at the age of 3 months, there was excessive bleeding from an injection site following administration of vaccines. Blood investigations showed the markedly changes in the haemogram and platelet count, USG reports showed that haemorrhagic cyst in bilateral ovary. There is no complete cure of this condition but the patient needs to be careful monitoring, it may lead to the life threatening of the patient. Symptomatic treatment can be provided such as contraceptive pills, antifibrinolytic drug and replacement therapy such as transfusion of plasma or factor VIII to control bleeding. Surgical treatment can be planned in case of failure of supportive therapy that is either oophorectomy or hysterectomy with oophorectomy.

Keywords: Von Willebrand Disease (VWD); Von Willebrand Factor (VWF); Excessive Menstrual Bleeding (Menorrhagia).

Introduction

Von Willebrand Disease (VWD) is the most common inherited bleeding disorder. It is occurred due to the deficiencies of Von Willebrand Factor (VWF). It is an adhesive and multimeric glycoprotein, which is essential for the normal haemostasis [1,2,3]. Von Willebrand Disease

was classified into three types i.e., type 1 VWD, type 2 VWD and type 3 VWD (Table 1). Type 3 Von Willebrand Disease is the most rare and severe form of the bleeding disorder which was associated with low or complete absent of von willebrand factor in the blood products and also associate with the deficiency of plasmatic factor VIII (FVIII) [4].

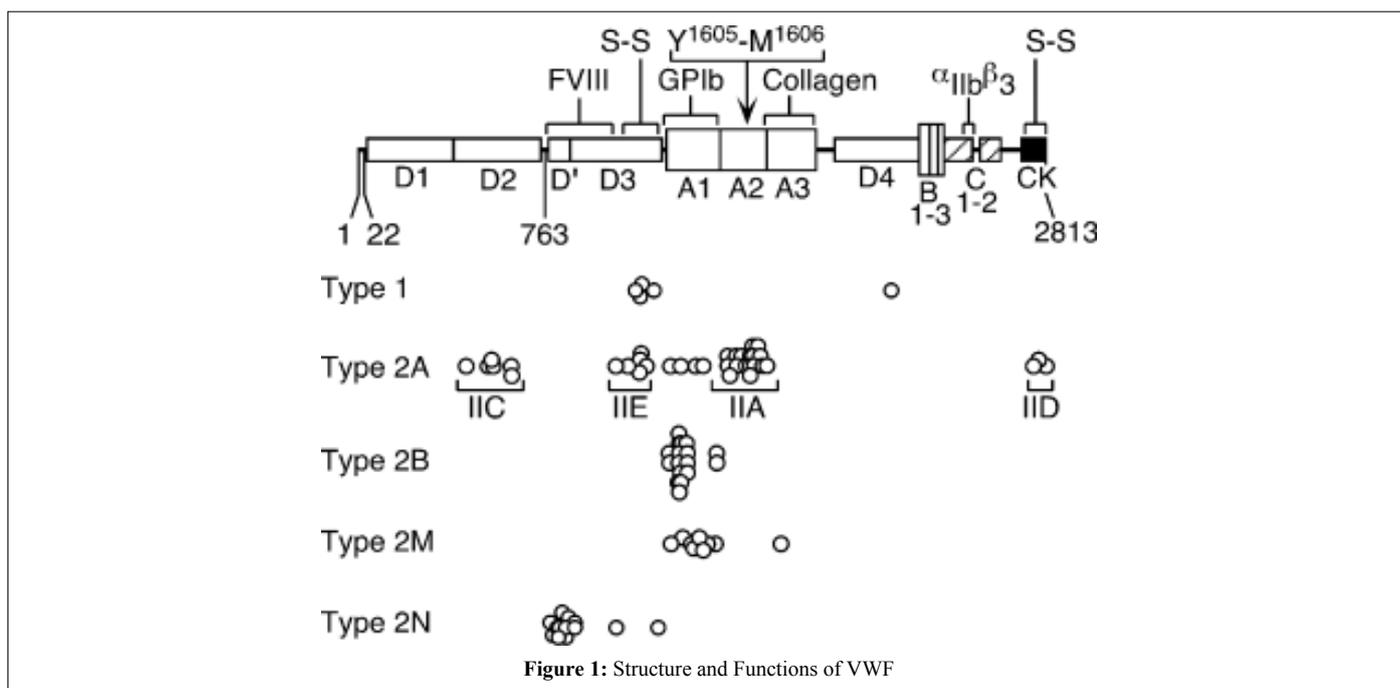
VWF – Von Willebrand Factor¹²

Structure and Functions of Von Willebrand Factor (VWF):

VWF is a multimeric plasma glycoprotein (GP) which composed of identical subunits of approximately 250 k Da. The multimers range in size from the dimers of approximately 500 k Da to species of > 10 million Da that contain > 40 subunits and exceed 2 micrometers in length. High - Molecular - Weight (HMW) VWF multimers mediate the platelet adhesions at sites of vascular injury by binding that to connective tissues and to platelet. VWF helps to bind and stabilize the blood clotting factor VIII. If any defect in the VWF that can cause the placental dysfunction which leads to bleeding or mild to moderately or severe hemophilia A or of both occurred [5]. Several binding functions have been limited to separate sites in the VWF subunit. Platelet GPIb networks with domain A1 and integrin $\alpha_{IIb}\beta_3$ interacts with an Arg - Gly - Asp sequence in domain C1. Fibrillar collagens interact mainly with domain A3, and collagen VI seems to bind domain A1. FVIII binds the N - terminal D'D3 region (Figure 1) [5].

Catabolism of Plasma VWF:

The VWF multimer rests on its size, interacts with the platelets and other cells, which affects to proteolysis and the rate of clearance from circulation. Under the high fluid shear stress multimers large enough to engage platelets may be overextended and exposed the Tyr¹⁶⁰⁵- Met¹⁶⁰⁶ bond



Type	Description
1	Partial quantitative deficiency of VWF
2	Qualitative VWF defects
2A	Decreased VWF – dependent platelet adhesion and a selective deficiency of high-molecular weight VWF multimers
2B	Increased affinity for platelet glycoprotein Ib
2M	Decreased VWF – dependent platelet adhesion without a selective deficiency of high-molecular-weight VWF multimers
2N	Markedly decreased binding affinity for factor VIII
3	Virtually complete deficiency of VWF

Table 1: The classification of von Willebrand Disease VWF – Von Willebrand Factor¹²

in VWF domain A2, which can be sliced by the ADAMTS-13 metalloprotease. By this mechanism ADAMTS-13 alters the initial VWF multimer distribution that is secreted into the blood, converting large multimers into smaller ones and producing characteristics of slice products. As a consequence, the electrophoretic pattern of plasma VWF display minor or satellite bands that edge the major multimer bands typical of endothelial cell VWF. VWF is also cleared from the blood with a half of life of 12-20 h by the process that looks to be relatively intensive to multimer size (Figure 2) [5].

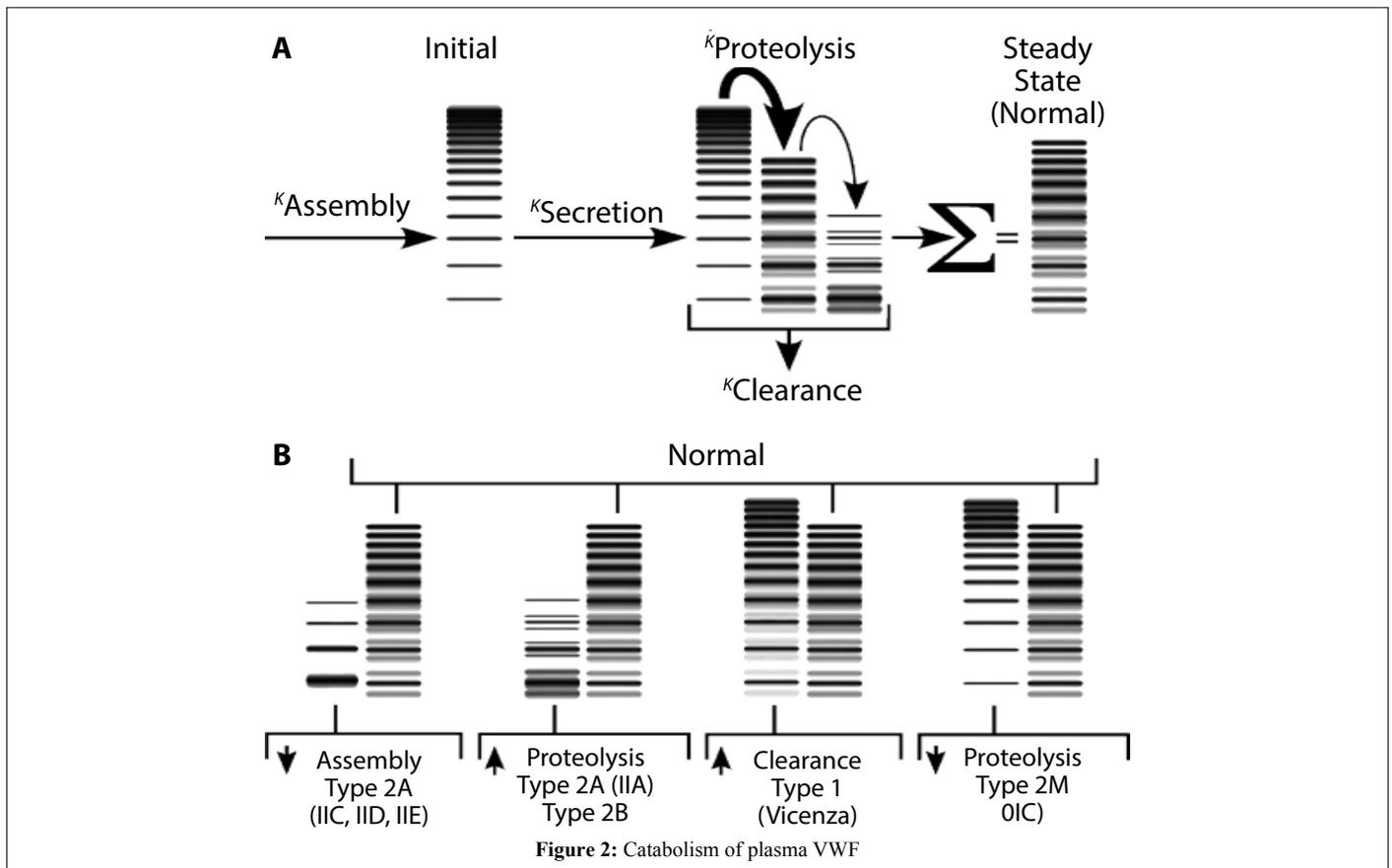
The concentration of plasma VWF is decided by the amounts of secretions and clearance and the multimer distribution reflects the balance between the mutimer assembly, clearance from the circulation and proteolysis by ADAMTS - 13. Mutations that affect these processes produce a type of VWD phenotypes. VWD type 3 is the almost complete absence of VWF. It is inherited as a recessive trait and heterozygous relatives usually have mild or no bleeding symptoms. In many cases, VWF: RCo; VWF: CB and VWF: Ag are < 5 IU dL⁻¹ and factor VIII levels are < 10 IU dL⁻¹. VWF mutations that cause VWD type 3 are usually boloney

mutations or frame shifts because of small insertions or deletion. Large deletions, splice site mutations and missense mutations are less common [5,6,7].

The prevalence of the disease varies from 0.1 - 5.3 per million which was raised with more consanguineous marriages. This type 3 VWD is an inherited autosomal recessive trait, with the heterozygous genotype which acts like either carrier (asymptomatic) or shows moderate to severe bleeding episodes [1].

Patient Information:

A 21 years old girl has known case of type 3 von Willebrand Disease and got admitted to gynaecology department at tertiary hospital with the history of excessive vaginal bleeding since last 3 months. During admission the old reports (confirmation test of von willebrand factor and factor VIII) were not available with patient. She was diagnosed as type 3 von Willebrand Disease with bilateral ovary cyst. There is no significant family history of genetic mutation or karyotyping of parents of patient to identify the cause of von willebrand disease. At the age of 3 months, she had persistent bleeding from an injection site following the administration of vaccines. There was prolonged prothrombin time (PTT) and blood sent for von willebrand factor gene sequence analysis to outside lab at New Delhi. She was diagnosed as von Willebrand Disease Type 3, at CMC Vellore Hospital [8]. She attained menarche at the age of 8 years and from that age every month she had excessive vaginal bleeding for seven days, approximately 200 - 300ml of blood loss that was identified by change of pads 5 to 6/day. She was treated in Jipmer Hospital at Puducherry, with factor VIII administration and 4 nos of fresh frozen plasma transfusion (4 times) to control the bleeding. Later, she was taken T. Ovrall L (Levonorgestral + Ethinyl Estradiol) as per



doctor's order which helps to decrease blood loss. She had taken that pills for over 10 years and she had menstruation yearly 3 to 4 times for 5 to 6 days. The blood loss markedly decreased when compared to previous cycles. At present she had admitted with the complaints of abdominal pain with menorrhagia since 9 days due to long term ingestion of hormonal therapy. There was approximately 250 to 300 ml of blood loss and 5 to 6 pads were changed per day.

Clinical Findings

On physical examination, she looks pallor, fatigue and had coated tongue and on abdominal palpation, identified warmth and tenderness on the lower abdominal area and mild abdominal pain with menorrhagia. On the day of examination, she had approximately 100ml of blood loss which is identified by no of pad changed per day, 3 - 4 pads. It was decreased when compared to the time of admission. She was on T. Tranexamic Acid 500mg TDS.

Diagnostic Assessment

Complete haemogram reveals that abnormal haemogram and platelet count (Table 2). Previous investigations of level of factor IX, XI and XII, vWF antigen and vWF activity was not with the patient side. Normally, vWF was completely absent in plasma of the type 3 VWD and the factor VIII was mostly in 2 - 20 IU/dl with the normal range 50 - 150 IU/dl. USG abdomen showed haemorrhagic cysts on the bilateral ovary. It measures that 2 to 3.5 cm on right side and 1.5 to 2 cm

on left side of the ovary. The thickness of endometrium was 13cm which was increased than the normal limits.

Therapeutic Treatment

The proposed treatment of this condition, closely monitoring of the patient and estimate the blood loss. Multivitamin tablets, T. Tranexamic Acid 500mg TDS and T. Ovril L OD which were helped to reduce the blood loss. At present admission she did not receive the fresh frozen plasma and factor VIII. She did not undergo for the recent genetic testing to know the von willebrand factors. The expectant treatment of this condition was surgical management to remove the cyst but which was not yet planned for her (Table 2).

Discussion

Von Willebrand Disease (VWD) type 3 is the rare condition which was characterized by the most severe form of bleeding disorder mainly due to little or complete deficiency of von willebrand factor (VWF) [1]. Von willebrand factor is a large, multimeric glycoprotein which is essential for the hemostasis. Von willebrand disease is an inherited autosomal recessive trait, with the estimation of prevalence approximately 1 in 1000 (0.1%) [2]. The incidence of the disease is very rare. The first case of this disease was identified and explained by Eric von willebrand in 1926 at Finland and during 1950s the similar cases were identified, *Inga Nilsson et. al.* reported that same disease in

Blood Parameters	Patient Value	Units	Normal Value
Complete Hemogram			
Hb	9.9	g/dl	Dec-14
W.B.C	9,900	/ μ L	4000-10000
Neutrophils	68	%	40-70
Lymphocytes	24	%	25-50
Monocytes	10	%	02-Oct
Eosinophils	3	%	01-Jul
R.B.C	3.43	106/ μ L	3.90 – 5.03
Platelet count	130	103/ μ L	150-450
Prothrombin Time	20	Secs	Dec-14
Biochemistry			
Urea	17	g/dl	15-45
Creatinine	0.4	g/dl	0.6 – 1.4
Na	135	mmol/L	135-145
K	3.6	mmol/L	3.5 – 4.5

Table 2: Blood Investigations

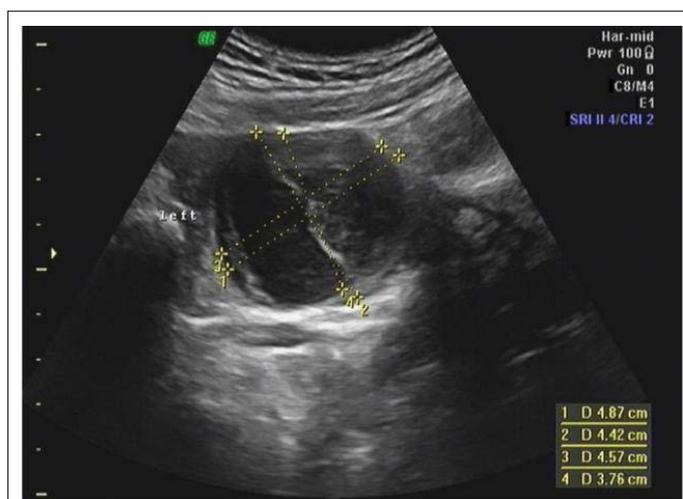


Figure 3: USG Scan report (Derived from Int J Women's Health. 2014; 6: 857-863. Published online 2014 Sep 23. Doi: 10.2147/IJWH.S47075) [14].

1957 at Sweden (Figure 3). It is a very rare condition which affects 0.1 - 5.3 person per million. The incidence is very high (5.3/ million) when compare with Europe and North America (1.51 & 1.38/million) [9,10]. The Etiology of this condition, it is caused by homozygous (for consanguineous marriage) or heterozygous (absence of symptoms or act as carrier) mutations in the von willebrand factor gene which affects the synthesis of glycoprotein or allele silencing [11].

The symptoms and severity of this conditions can differ from one person to another for e.g. Some individual will be asymptomatic or only mild symptoms and others may have moderate to severe bleeding complications. In type 3, severe symptoms only most likely to occur, that is women may have heavy and excessive bleeding during the menstrual period (menorrhagia), if not treated properly that lead to anaemia and iron deficiency. The more serious of this condition are developing multiple hematomas in the internal organs if not noticed earlier it lead to life threatening to the patients [12]. The diagnosis of this conditions based on the identification of the symptoms. The severe form of VWD (type 3) may be

identified during the infancy period. It can be ruled out by detailed family history, and a thorough clinical evaluation. It can be diagnosed easily when compared to the other type of VWD by the severe deficiency of the VWF and factor VIII. The plasma value of VWF is almost absent in the type 3 VWD and factor VIII level is mostly 2 -20 IU/dl (the normal range: 50 - 150 IU/dl) [1]. Complete blood count to check the hemogram and platelet count. Usually the prothrombin time is normal in patient with VWD. Molecular genetic testing is used to confirm the disease by measure the amount of VWF in blood and identify the characteristic of VWF gene mutation [6,7].

There is no exact cure for this type of disease conditions, but symptomatic treatment will be given based on the severity on the conditions. If there are severe bleeding episodes, the patient should receive the prompt treatment to control the blood loss. Replacement therapy that is either frozen plasma or factor VIII to be replaced in case of severe bleeding for the type 3 VWD. Drug Desmopressin is ineffective in this type 3 VWD. In additional, women with type 3 VWD treated with contraceptive pills which will improve the VWF level in blood and control the heavy bleeding during menstrual period. Antifibrinolytic agent such as aminocaproic acid (Amicar) and tranexamic acid which can be given for the treatment of bleeding episode. Genetic counselling can be useful for the inherited autosomal recessive trait family members. Surgical procedure may be required in case of trauma or injury, hematoma or cyst formation [5,6,7,13].

Conclusion

This case denotes the clinical presentation and diagnosis of the patient with known type 3 VWD and bilateral ovarian cyst. It is the very rare condition and identifying this type of condition is quite risk. As well as, women are more risk when compare to men because every month women required either plasma transfusion or factor VIII due to excessive menstrual bleeding without any trauma. It is an inherited autosomal recessive trait that is this condition is present first time in their family as a result of mutation in germ cells which is adding further uniqueness of this case.

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