

Use of Mirena (Levonorgestrel-releasing intrauterine system) in menorrhagia in a young female with von Willebrand disease (vWD) Type 3 - A case report

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Abstract

von Willebrand disease (vWD) is a bleeding disorder that is predominantly attributable to reduced levels of von Willebrand factor (vWF) activity. vWD prevalence is 1% in the population and vWD Type 3 is very rare. vWD Type 3 is inherited as autosomal recessive manner and accounts for less than 5% of all cases. Individuals with vWD type 3 can have a severe internal and joint bleeding.

However, type 3 and type 2 variants are extremely difficult to manage and there is no guarantee that haemostasis will be achieved even when plasma concentrations have apparently been corrected into the normal range.

We report a female child aged 10 years presented to us with heavy menstrual bleeding for three days which continued for another seven days. This episode was after recent onset of menarche and was diagnosed as having vWD Type 3. It was considered as a life threatening bleeding.

Immediate and long term management of this patient with a major bleed was a daunting task.

She was treated with Intermediate purity factor viii/ factor viii (cryoprecipitate), activated factor vii, Blood and antifibrinolytics.

Long term endometrial suppression was the key to hinder excessive bleeding during menstruation (which could be life threatening) as she would need prophylaxis during each episode. Selecting the correct method which suits her best was not without difficulty.

Intrauterine use of Mirena (levonogestrel-releasing intrauterine system-LNG-IUS)

was a better option and there are very few reports if at all of its use in a similar situation. We have used it as a novel method to suppress excessive menstrual bleeding (long term) in this patient with von Willebrand disease type 3.

Key Words: von Willebrand disease, Menorrhagia, Mirena

activity <0.30 iu/ml is usually associated with bleeding symptoms.

Its prevalence is about only 1%, and has been detected in women with increased bleeding tendency during menstruation. Type 1 represents 60%-80% of the cases. Type 2(2A, 2B, 2M & 2N) is about 20-30%. Type 3 accounts for less than 5% of all the cases and inherited as autosomal recessive manner where as other types are inherited as autosomal dominant manner. Acquired vWD occurs in individuals over 40 years with no previous bleeding history.

However, type 3 and type 2 variants are extremely difficult to manage and there is no guarantee that haemostasis will be achieved even when plasma concentrations have apparently been corrected into the normal range⁴.

CLINICAL MANIFESTATIONS

VWD Type 1 manifests as mild mucocutaneous bleeding. i.e. bruising and epistaxis.

Type 2A, 2B and 2M vWD individuals usually manifest mild to moderate mucocutaneous bleeding where as type 2N vWD is similar mild hemophilia A which includes excessive bleeding at the time of surgery. Acquired vWD individuals also present with mild to moderate bleeding. Individuals with vWD type 3 have a severe internal and joint bleeding⁶.

Type 3 is diagnosed when vWF Antigen (<12%) and vWF Activity (<3.5%) are very low.

Current recommendation (British Society for Haematology Guideline 2014) is that prophylactic treatment should be offered for individuals with type 3 with spontaneous haemarthroses, muscle bleeds, severe epistaxis and women with menorrhagia.

Treatment modalities include desmopressin, tranexamic acid, platelets,

INTRODUCTION

von Willebrand disease (vWD) is a bleeding disorder that is predominantly attributable to reduced levels of Von Willebrand factor (vWF) activity. It is the bleeding disorder that is commonly seen in women. vWF is a large and complex plasma glycoprotein that is essential for normal haemostasis. The plasma level of VWF in normal individuals varies from 0.40 to 2.40 iu/ml³, and VWF levels are about 25% lower in blood group O individuals than in non-O³. A VWF

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Intermediate purity FVIII-vWF or high purity vWF concentrate and menorrhagia should also be managed with hormones.

CASE PRESENTATION

We report a female child aged 10 years who had three days of spotting followed by heavy menstrual bleeding for 7 days with the onset of menarche. It was settled with oral norethisterone and tranexemic acid. Patient was started on OCP for nearly 3 weeks and during this period she had irregular per vaginal (PV) bleeding which was mild.

With her next menstrual period, she had heavy menstrual bleeding for 3 days which continued for another 7 days. She was admitted to the Gynaecology ward from the haematology clinic for further investigation and management and reviewed regularly by the haematology team. She was diagnosed as vWD type 3. This episode of menstrual bleeding was considered as a life threatening bleeding (Hb 12.9 to 7.2).

At the age of 2 ½ years she was presented to Sri Jayawardenepura General Hospital for excessive bleeding following cut injury to the head after trauma, which lasted more than 5 hours. She was bleeding from the site heavily disproportionate to the site and size of cut injury and it had taken exceeding long time to achieve haemostasis.

She had ecchymotic patches and gave a history of easy bruising and on and off gum bleeding. There was no bleeding into joints and no features suggestive of the same. She had no bleeding or haematoma formation after intramuscular (IM) injections (EPI Schedule).

She had no known drug or food allergies and she was born to nonconsanguinous parents.

She was afebrile and she was haemodynamically stable. There was no hepatosplenomegaly.

She was investigated at that time and managed as von Willebrand disease type 1 with DDAVP (Desmopressin) and Partial purified factor V111 concentrate.

Instructions were given to avoid contact sports, IM injections, NSAIDS and to maintain good oral hygiene. Advice was given to get subcutaneous vaccines only.

Family screening was normal. Genetic Screening of the family and the patient was not carried out.

Since her first presentation until now she was asymptomatic.

On admission she was afebrile, pale and dehydrated. She was haemodynamically stable. There were no ecchymotic patches or any signs or symptoms of bleeding into the joints. There was no hepatomegaly but mild splenomegaly. Other examination findings were unremarkable.

INVESTIGATIONS

Blood group- B^{+ve}, Anti Le^a + Anti Le^b, DAT- Negative, Rh phenotype- R₁rEE, Lewis phenotype Le (a₋ b₋), FBC-WBC 11*10³mm³, HB-7.2g/dl, Plt-201*10³, CRP: < 5 mg/L, ESR: 20 mm/1st hour, UFR: pus cells 2-3/field and red cells 20-30/field, USS- Abdomen-No lymphadenopathy detected, prominent spleen, Liver, kidneys, pancreas and gallbladder are normal.

MANAGEMENT

Following blood and blood products and Factor concentrates were given.

Immunate (Intermediate purity factor V111) = (250 IU FV111/190 IU VWF), Activated Factor V11 (Novo seven), Cryoprecipitate, Blood (RCC), Platelets.

In addition to the above she was treated with IV tranexemic acid, iron supplements, folic acid, Vit C, OCP one tab daily and norethisterone 5mg tid.

Subcutaneous Jadelle (levonogestrel) was inserted aiming for long term control of menorrhagia but did not reduce blood loss with menstruation. Therefore Intrauterine Mirena was inserted which relieved her from heavy menstrual loss.

DISCUSSION

(Based on British Society for Haematology guideline on von Willebrand disease – September 2014¹)

IMMEDIATE MANAGEMENT

It was a life threatening blood loss and in consultation with haematologist we had to transfuse Immunate (Intermediate purity factor V111) higher doses of which could have led to high levels of FV111 and hence thrombosis⁵. This is due to unavailability of FV111 assay and vWF in the hospital.

According to B-S-H Guideline 2014, platelets were transfused in addition to blood and cryoprecipitate (as FV111).

Activated Factor V11 (90ug/kg) was also transfused to control bleeding¹.

Special coagulation test profile for von Willebrand Disease.

Test	Value	Control	Normal Range
APTT	62.7 sec	33.5 sec	25.4-38.4 sec
PT	14.9 sec	13.1 sec	11.8-15.1 sec
Factor V111	0.83%	107%	50-150%
vWF Antigen	<12% Lower detection limit-12%	105%	(61.3-157.8%)
vWF Activity	<3.5% Lower detection limit-3.5%	97.5%	(49.2-169.7%)

Antifibrinolytic tranexamic acid was given intravenously (IV) (but it is not without side effects.)

Thereafter cryoprecipitate, blood and platelets were given in decrement doses as the bleeding was settling.

LONG TERM AND HORMONAL MANAGEMENT

There are few case reports where danazol, combined oestrogens and progestogens, GnRH analogues are being used but all of them carried their own side effect profile.

Since she attained menarche there were very limited options available. Our aim was to suppress the endometrium immediately and long term.

Surgical options like endometrial ablation and uterine artery ablation were not feasible due to young age and the bleeding disorder.

ORAL PROGESTOGENS-NORETHISTERONE

Norethisterone converts the endometrium from the proliferative to the secretory phase. It may also have some estrogenic, anabolic and androgenic activities. The contraceptive effects are due to negative feedback inhibition of pituitary gonadotropin, whereby it prevents ovulation. This was useful as a temporary measure to suppress menstruation but could not use long term due its side effects.

COMBINED OESTROGENS/ PROGESTOGENS

Thins out endometrium but not very effective in long term due its side effects.

Danazol- Danazol acts by suppressing the pituitary-ovarian axis and inhibiting the pituitary output of gonadotropins, hormones that increase in the endometrium. It is a chemical derivative of testosterone that inhibits ovulation and reduces estrogen levels.

But we could not use it because of virilization effects of danazole.

GONADOTROPIN-RELEASING HORMONE (GnRH) ANALOGUES

GnRH analogues are competitive agonists at GnRH receptors in the pituitary. GnRH-releasing cells are eventually desensitized,

resulting in a hypogonadotropic state, which causes hypogestrogenism, endometrial atrophy and amenorrhea.

They have been known to cause bone demineralization of up to 5% in women taking them for over 6 months. Therefore its usefulness in long term endometrial suppression was not feasible due to growing age of this child.

JADELLE

Subcutaneous implants of 75mg of levonorgestrel-2 implants active for 5 years.

Release rate of 100ug/day first month, 40ug/day within a year and 30ug/day within 3 years and about 25ug/day within five years.

INTRAUTERINE PROGESTOGENS

Levonorgestrel-releasing intrauterine system (Mirena-52mg) releases 20ug/day for 5 years. It leads to thinning and atrophy of the endometrial lining (glandular and stromal tissues) as the endometrial oestrogens are suppressed by levonorgestrel's effect on uterus and therefore reduction in menstrual bleeding. In addition ovulation is inhibited in some women. BSH guideline-2014 recommends considering Mirena as a method of hormonal management^{1,7,8}.

Norethisterone was given as a bridging therapy for Mirena.

CONCLUSION

According to Society for Haematology guideline on von Willebrand disease – September 2014 a patient with vWD type3 would need regular prophylaxis during each menstrual cycle. We have averted such massive transfusions as well as the cost involved by using Mirena as major part of hormonal management. We have used it to suppress excessive menstrual bleeding (long term) in this patient with von Willebrand disease type 3.

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