Hemophilia B in a Female Adolescent: A Case Report

Joanna Francesca C. Nayal, MD and Ma. Susan C. Balete, MD, FPOGS, FPSUOG, FPSSTD*
Department of Obstetrics and Gynecology, Our Lady of Lourdes Hospital

ABSTRACT

Hemophilia is a relatively rare bleeding disorder. It is an X-linked hereditary bleeding disorder caused by a deficient or defective coagulation factor VIII (Hemophilia A) or factor IX (Hemophilia B). Hemophilia A is more common than Hemophilia B. The X-linked inheritance pattern results in men expressing the disease and women typically being carriers. Under rare circumstances a woman can also show a bleeding phenotype.

A 13 year-old female presented with profuse vaginal bleeding. She had history of several hospital admissions because of bleeding manifestations like hematuria and epistaxis. Based on the pedigree analysis and results of factor IX assay tests she was diagnosed to have Hemophilia B of moderate severity. She was given hormonal and non-hormonal treatments as well as blood transfusions which stop the bleeding and corrected the anemia. A multidisciplinary approach of management involving the gynecologist, hematologist and a geneticist will be beneficial to the patient.

The inheritance, clinical manifestations, diagnosis and treatment of Hemophilia B in a female adolescent are discussed.

Keywords: Hemophilia B, Lyonization, Abnormal uterine bleeding in adolescents

INTRODUCTION

Anovulation and coagulation disorders are the two common causes of heavy menstrual bleeding in adolescents. Heavy menses is defined as menstrual blood loss greater than 80 ml.[1] Approximately 95% of heavy menstrual bleeding in adolescents is due to anovulation[1] which is mainly due to the immaturity of the hypothalamic-pituitary-ovarian (HPO) axis. Coagulation disorders can be inherited or acquired and may be caused by thrombocytopenia, platelet function disorders or clotting factor deficiencies. When there is a personal or family history of bleeding, an inherited bleeding disorder should be suspected. Von Willebrand Disease (VWD) is the most common inherited bleeding disorder. Among adolescents with heavy menstrual bleeding, the prevalence of VWD is 5-36% and that of platelet dysfunction is 2-44%. Clotting factor deficiency has a prevalence of 8% compared to that of thrombocytopenia which is 13-20%.[1]

Inherited bleeding disorders affect both men and women. Symptoms are quite variable and depend on the type and severity of the disease. For the same disease severity, usually women are more symptomatic because of excessive menstrual bleeding and peripartum hemorrhage.

Our patient has a family history of Hemophilia B which is an X-linked hereditary bleeding disorder caused by a deficient or defective coagulation factor IX. Due to its recessive X-chromosomal inheritance pattern, mostly males are affected and females are usually "carriers" of the hemophilia gene and are generally asymptomatic. However, in rare instances some carriers have low levels (<40% of the normal) of factor IX that are comparable with males that have Hemophilia B. These females have hemophilia.

This case report is presented to make clinicians be aware that Hemophilia is an inhertited bleeding disorder that affects both men and women. It also aims to discuss the inheritance, clinical manifestations, diagnosis and management of a rare case of Hemophilia B in a female adolescent.

CASE REPORT

Our patient (Figure 1) was a 13 year-old, Roman Catholic, from San Juan Metro Manila who was admitted for the thirteenth time at our institution last November 2, 2013 because of profuse vaginal bleeding.

The patient had been having regular menstruation until thirteen weeks prior to admission when she did not have her monthly period. No consultation was done.

Nine weeks prior to admission, she had vaginal spotting for one week which amounted to less than one panty liner per day. No consult was done nor any medication taken.

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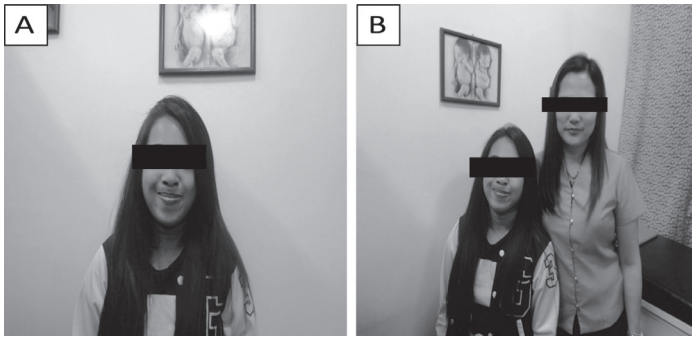


Figures 1A. The patient. **1B**. Our patient with her mother.

Eight weeks prior to admission, she noted an increase in the amount of vaginal bleeding which amounted to three pads per day (fully soaked), accompanied with passage of blood clots. There were no other accompanying signs and symptoms. The vaginal bleeding lasted for one week and was followed by vaginal spotting (less than one panty liner per day) which spontaneously stopped after a week. No consultation was done.

Two weeks prior to admission, there was recurrence of vaginal spotting amounting to less than one panty liner per day. No consultation was done.

Thirteen days prior to admission, patient had vaginal bleeding amounting to three pads per day (fully soaked). There were no associated signs and symptoms.

Eleven days prior to admission, due to the persistence of vaginal bleeding, consult was done with the attending obstetrician-gynecologist. The vaginal bleeding at that time amounted to less than one pad per day. Transrectal ultrasound done showed a normal sized anteverted uterus, thickened endometrium and a normal left ovary. The right ovary was not visualized. Complete blood count showed anemia (Hgb=107, Hct=0.32). She was given Medroxyprogesterone acetate (Provera) 10mg once a day for five days, and Ferrous sulfate one tablet once a day. She was advised to come back if with withdrawal bleeding.

Vaginal bleeding stopped until four days prior to admission, when the patient had withdrawal bleeding initially amounting to two pads per day. The amount of bleeding increased to one to two baby diapers per day (fully soaked). No consultation was done.

Few hours prior to admission, due to the persistence of profuse vaginal bleeding, consultation was done and she was advised admission.

Review of systems was unremarkable. Family history was positive for a bleeding disorder. The patient's grandfather was Spanish and had Hemophilia. He married a Filipino and they had six children (three males and three females). The eldest daughter was married and had four children (two females and two males), the youngest of whom was a male with Hemophilia B. The second among the six children was a male who got married and had a boy (9 years old) and a girl (8 years-old). The third of his six children was the mother of our patient. Our patient was diagnosed to have Hemophilia B and she had no other siblings. The fourth of the six children was a male who married and had a daughter (5 years-old). The fifth of the six children was a female who married and had two boys (4 years-old and 3 years-old). She is now pregnant and ultrasound examination showed a male fetus. The four year old boy had bleeding tendencies (easy bruisability, longer time for wound to stop bleeding). The last among the six children was a male and not married. (Figure 2)

Maternal history showed that the mother had intrauterine fetal demise (6-7 months AOG) during her first pregnancy. She underwent Cesarean Section due to Placenta Previa Totalis. During her second pregnancy, she

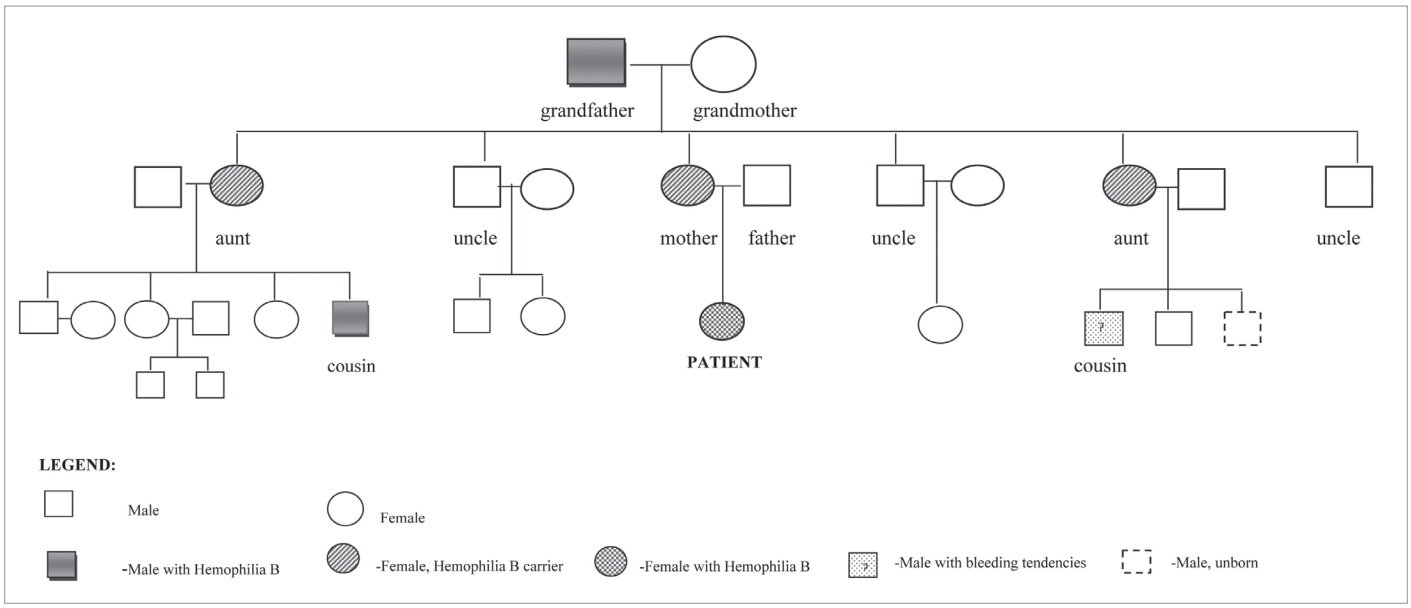


Figure 2. Pedigree Analysis of Patient.

gave birth to our patient via Repeat Cesarean Section with no fetomaternal complications noted. She had Dilatation and Curettage during her third pregnancy because of Missed Abortion.

Past medical history showed that our patient had twelve previous admissions in our institution. Majority of the previous hospitalizations were due to Acute gastroenteritis with moderate dehydration. At four years old, she was admitted because of Acute Bacterial Meningitis secondary to Mastoiditis and Sinusitis. She had Bronchopneumonia when she was seven and eight years old. At eight years and eleven months old, she was hospitalized because of fever, ear pain with bleeding on the left ear, and epistaxis. At that time, she was diagnosed with Acute Bacterial Bronchopneumonia, bilateral; Acute Otitis Media, AU and Recurrent Sinusitis. When she was nine years and ten months old, she had joint pains and hematuria. Ultrasound of the kidneys, ureters and bladder showed normal sized kidneys, mild caliectasia, right and insignificant urinary retention. Creatinine was normal. She was referred to a nephrologist and a hematologist. Prothrombin Time was normal (13.6 secs) and Activated Partial Thromboplastin Time (APTT) was prolonged (86 secs). Factor VIII assay test showed normal result. Factor IX assay test showed low level (Table 1). She was diagnosed to have Hemophilia B, moderate. She was transfused with 5 units of Fresh Frozen Plasma and 8 units of Cryosupernate. At eleven years and three months old, she was again admitted because of epistaxis. Factor IX assay test showed low level (Table 2). She was transfused with 2 units of Fresh Frozen Plasma. When she was eleven years and six months old she had swelling of the right elbow and left knee as well as epistaxis. Factor IX level was low (Table 3) and she was transfused with 8 units of Fresh Frozen Plasma. She was admitted when she was thirteen years old because of swelling of the left upper extremity and left lower extremity including the left elbow and left knee. She was transfused with 4 units of Cryosupernate.

Table 1. Factor Assay (1/30/2010)

Component		Control	
Factor VIII	93.7	102.5	(Reference range 70-150% of normal)
Factor IX	1.6	90.7	(Reference range 70-120% of normal)

Table 2: Factor IX Assay (7/19/2011)

Component		Control	
Factor IX	2.4	95.5	(Reference range 70-120% of normal)

Table 3: Factor IX Assay (10/26/2011)

Component		Control	
Factor IX	3.3	109	(Reference range 70-120% of normal)

Outpatient medical history showed that when patient was 4 years-old, she had tooth extraction. She had gum bleeding for seven days. No consult was done. At six years old, she had hematoma on the left deltoid after an intramuscular injection of tetanus vaccine. Hematoma resolved after two weeks. At seven years-old, she had contusion on her left breast which resolved after two days. No history of trauma was elicited at that time. When she was 9 years-old, she had epistaxis upon waking up, which spontaneously resolved after 10 minutes. Consult with her pediatrician was done and she was referred to a pediatric hematologist. Unfortunately the patient failed to consult the hematologist.

Our patient was a Grade 6 student in a private school with average grades. She had good interpersonal relationship with her family and they were supportive of her condition. She had complete immunizations (Table 5).

She had menarche at 12 years old. Subsequent menstruations were regular, occurring every 28-30 days, of 3-4 days duration, using 3-4 pads per day, with no accompanying dysmenorrhea .

On admission, patient was tachycardic (HR=110bpm). Both height and weight were below the ideal for her age (weight=38.5kg (85lbs); z score=-1; P=<3%), (Height=142 cm (4'8"); z score = -2 to -3; P = <3%). She had pale palpebral conjunctiva. Sexual maturity rating was Tanner Stage 3. External genitalia was grossly normal. There was blood coming out of the vaginal introitus. Rectal examination showed a normal sized anteverted uterus with no palpable mass nor tenderness on both adnexal areas. The rest of the physical examination was unremarkable.

Anemia due to Abnormal Uterine Bleeding secondary to Hemophilia B was considered on admission. A referral to the Pediatric service for evaluation and co-management was made. Complete blood count showed anemia (Hgb=75, Hct=0.22) (Table 6). Platelet count (Table 6) and Prothrombin time (Table 7) showed normal results. Activated partial thromboplastin time was prolonged (66.2 secs) (Table 7). Factor IX assay test showed low level (3.4% of normal) (Table 4).

Table 5. Immunization History

Immunization	Primary	Booster
BCG	1 month old	
DPT	2,3,4 mo.	18 mo., 6 y/o
IPV	2,3,4 mo.	18 mo., 6 y/o
Hepatitis B	2,3,4 mo.	18 mo., 6 y/o
Hib	5,6,7 mo	19 mo.
Measles	8 mo.	
MMR	12 mo.	4 y/o

Table 4. Factor IX Assay (11/5/2013)

Component		Control	
Factor IX	3.4	96.5	(Reference range 70-120% of normal)

Table 6. Laboratory examinations

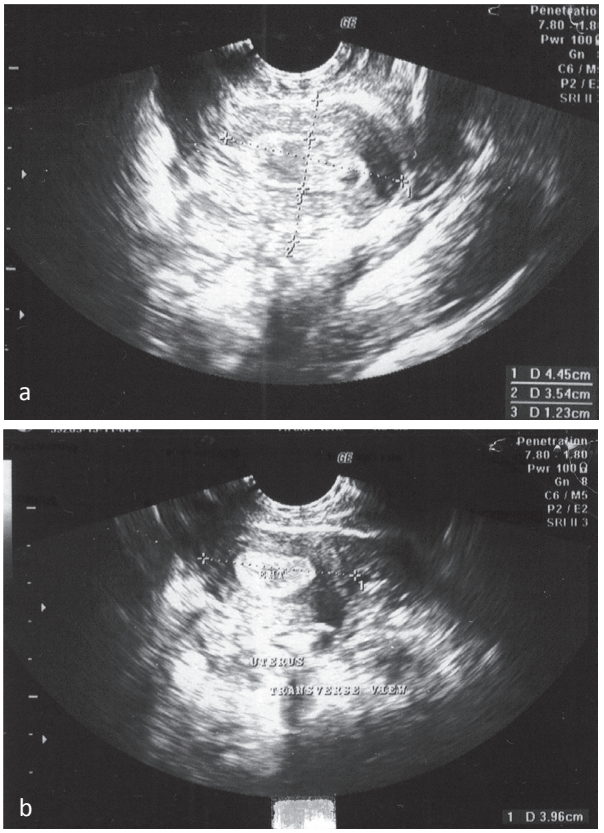
CBC	11/2/2013	11/4/2013
Hemoglobin	75 g/L	131.0 g/L
Hematocrit	0.22 l	0.39
Erythrocyte No.Conc.	2.53 x (10) 12/L	4.37 x (10) 12/L
MCV	89.0 fl	88 fl
MCH	29.6 pg	29.9 pg
MCHC	33.3 g/dl	34.0 g/dl
RDW	15.5%	14.9%
Leucocyte No.Conc.	5.6 x (10) 9/L	8.3 x (10) 9/L
Segmenters	0.63	0.56
Lymphocytes	0.32	0.04
Monocytes	0.01	0.36
Eosinophil	0.04	0.4
Platelet	278.0	278.0

Table 7. Coagulation assay

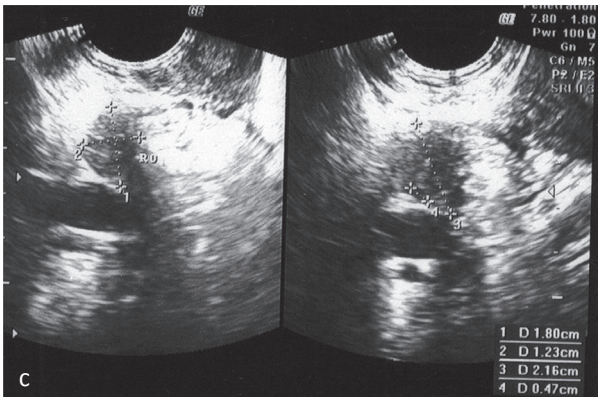
	11/2/2013
Prothrombin Time	12.8sec (Normal values: 10-14sec)
Control	11.21sec
INR	1.19
Protime activity	73.9 %
APTT	66.2sec (Normal values: 28-36)
Control	33.8sec

She was transfused three units of packed RBC. Repeat complete blood count showed normal results (Hgb=131, Hct=0.34) (Table 6). Intravenous antifibrinolytic agent (Tranexamic acid) and oral iron preparation were given. Transrectal ultrasound done showed a normal sized anteverted uterus, thickened endometrium and normal ovaries (Figure 3). She was started on combined oral contraceptive (Levonorgestrel 150 mcg and Ethinyl estradiol 30mcg) using this regimen: 1 tablet every 6 hours for 4 days; 1 tablet every 8 hours for 3 days; 1 tablet every 12 hours for 2 days; and 1 tablet once a day for 21 days. On the third hospital day, she had vaginal spotting which eventually stopped. She was discharged improved on the fourth hospital day.

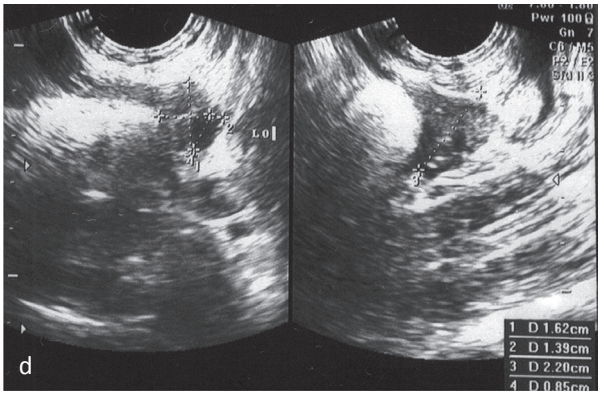
At present, the patient is on combined oral contraceptive pills. She is taking Tranexamic acid and iron preparation during her monthly period. She has regular monthly menstruation, of 3-4 days duration, using 2-3 pads per day, with no accompanying dysmenorrhea.



Cervix - measures 2.16cm x 2.09cm x 2.04cm
Uterus - anteverted, measures 4.45cm x 3.96cm x 3.54cm, homogenous
Endometrium 1.23 cm thick, hyperechoic, smooth



Right ovary - measures 1.80cm x 2.16cm x 1.23cm, biggest follicle measures 0.47cm



Left ovary - measures 1.62cm x 2.20cm x 1.39cm, biggest follicle measures 0.85cm

Figures 3a-d. Transrectal ultrasound (11/04/2013)

IMPRESSION: Normal sized anteverted uterus with thickened endometrium. Normal ovaries

DISCUSSION

Heavy menses is defined as menstrual blood loss greater than 80 ml.[1] According to a committee opinion from the American College of Obstetricians and Gynecologists, adolescents usually have their menarche between 11 and 14 years of age. The normal cycle length is between 21 to 45 days with length of period of 7 days or less. The events in a normal menstrual cycle occur in an orderly and sequential pattern because of the effect of the hypothalamic-pituitary-ovarian axis (HPO axis). In adolescents the HPO axis usually takes time to mature so much so that in the first two years after menarche, 55-82% of cycles are anovulatory. By the fourth and fifth years after menses, only 20% of menstrual cycles are anovulatory.[1]

Anovulation and bleeding disorders are the two common causes of heavy menstrual bleeding in adolescents[2,3] as compared to the adult population wherein pelvic pathology such as fibroids and polyps being the common causes.[1]

Approximately 95% of heavy menstrual bleeding in adolescents is due to anovulation.[1] Without ovulation, progesterone is not produced, leading to a state of unopposed estrogen. Unopposed estrogen stimulate endometrial growth until such time that the endometrium outgrows its own blood supply. The endometrium becomes excessively thick and unstable until the lining breaks down irregularly and unpredictably. This results to heavy and prolonged menstruation.

Coagulation disorders are the second most common cause of heavy menses among adolescents.[1,2] A normal number of platelets, normal platelet function and normal levels of clotting factor are needed for hemostasis to occur during menstrual period. Bleeding disorders can be inherited or acquired, and may be due to decrease in platelet count, platelet function disorders or clotting factor deficiencies. A congenital bleeding disorder may be suspected when there is a personal or family history of bleeding.[3] An acquired bleeding problem is more likely when there are medications that inhibit platelet function, when the patient is on anticoagulant therapy or when there are comorbidities like renal disease, liver disease and hypothyroidism.[4] Hemophilia is usually inherited, meaning that it is passed from parent to child through the parent's gene.[5] Von Willebrand Disease (VWD) is the most common inherited bleeding disorder.[1,6] Among adolescents with heavy menses, the prevalence of VWD is 5-36%, platelet dysfunction is 2-44%, clotting factor deficiency is 8% and that of thrombocytopenia is 13-20%.[1] The prevalence of heavy menses among Hemophilia carriers (reduced levels of Factor VIII or IX) is represented to be 10-57%.[1] Our patient has normal platelet count, bleeding time, clotting time, prothrombin time, factor VIII levels but decrease levels of factor IX and prolonged activated partial thromboplastin time.

Hemophilia is an X-linked hereditary bleeding disorder caused by a deficient or defective coagulation factor VIII (Hemophilia A) or factor IX (Hemophilia B).[7] The role of the coagulation system is to produce a stable fibrin clot at sites of injury. The clotting mechanism has two pathways namely intrinsic and extrinsic. The intrinsic system is initiated when factor XII is activated by contact with damaged endothelium. In conjunction with high-molecular-weight kininogen (HMWK), factor XIIa converts prekallikrein (PK) to kallikrein and activates factor XI. Activated factor XI, in turn, activates factor IX in a calcium-dependent reaction. Activated factor IX (Factor IXa) binds phospholipids. Factor X is activated on the cell surface. Activation of factor X involves a complex of factor IXa, thrombin-activated factor VIII, calcium ions, and phospholipid. In the extrinsic pathway, the conversion of factor X to factor Xa involves tissue factor (TF) or thromboplastin, factor VII and calcium ions. Tissue factor is released from the damaged cells and acts as a cell surface receptor for factor VII with its resultant activation. It also absorbs factor X to enhance the reaction between factor VIIa, factor X, and calcium ions. Factor IXa and factor XII fragments can also activate factor VII. In the common pathway, factor Xa (generated through the intrinsic or extrinsic pathways) forms a prothrombinase complex with phospholipids, calcium ions and thrombin-activated factor Va. The complex cleaves prothrombin into thrombin and prothrombin fragments 1 and 2. Thrombin converts fibrinogen into fibrin and activate factor VIII, factor V, and factor XIII. Fibrinopeptides A and B that resulted from the cleavage of peptides A and B by thrombin, cause fibrin monomers to form and then polymerize into a meshwork of fibrin. The resultant clot is stabilized by factor XIIIa and the cross-linking of adjacent fibrin strands (Figure 4). Factor VIII and Factor IX circulate in an inactive form. When activated, these 2 factors cooperate to cleave and activate Factor X, a key enzyme that control the conversion of fibrinogen to fibrin. The lack of either of these factors may significantly impair clot formation resulting to clinical bleeding.

Hemophilia is a relatively rare bleeding disorder.[8] It affects people from all racial and ethnic groups. There are two types of hemophilia: Hemophilia A and Hemophilia B. Those with Hemophilia A do not have enough clotting factor VIII and those with Hemophilia B do not have enough clotting factor IX. Factor IX is located on the long arm of the X chromosome in band q27.[9] Hemophilia A is four times more common than Hemophilia B. Based on

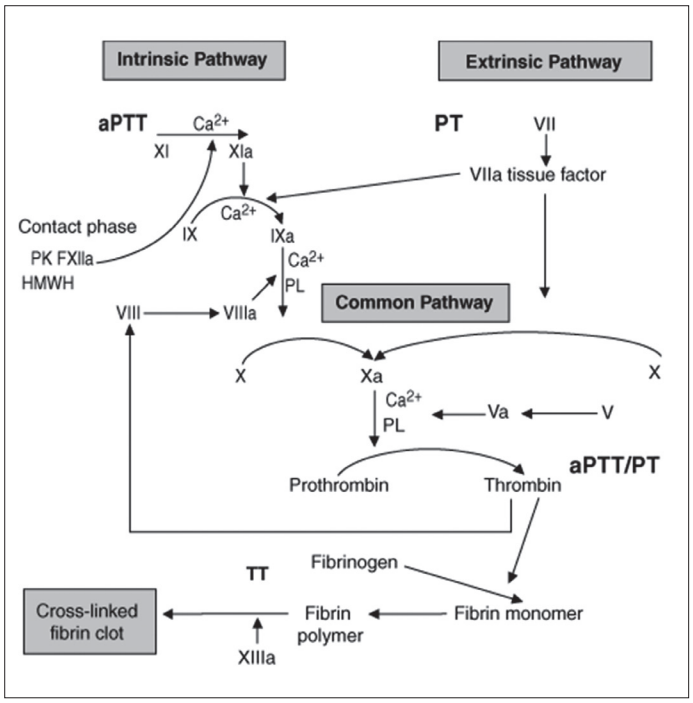


Figure 4. Coagulation Cascade[12]

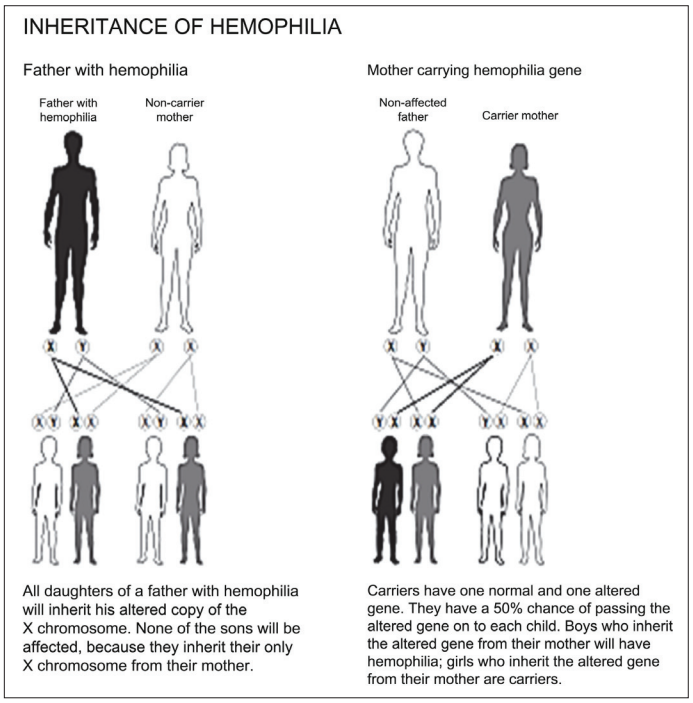


Figure 5. Inheritance of Hemophilia[5]

the Annual Global Survey done by the World Federation of Hemophilia in 2011, the Philippines reported that 1131 out of the total population of 94,852,036 have Hemophilia (about 0.0012%).[10] The type of healthcare system in a member country can influence the quality of data submitted in the survey. A country with universal health care may be more likely to identify patients with Hemophilia even if they don't require treatment while in countries with different health care systems, it is likely that those who are asymptomatic and do not require treatment may not be identified. Based on the survey, of the 1131 reported cases of Hemophilia in the Philippines, 945 (83.6%) have Hemophilia A, 145 (12.8%) have Hemophilia B, while 41 (3.6%) have unknown type of hemophilia.10 According to Przkora R, Euliano TY, Roussos-Ross K, et.al., Hemophilia A and B have a prevalence of 1 in 10,000 and 1 in 100,000 respectively.[11] In an article written by Zaiden R, Dronen S, et.al., the incidence of Hemophilia B is estimated to be approximately 1 case per 25,000-30,000 male births, while its prevalence is 5.3 cases per 100,000 male individuals with 44% of them having severe disease.[9] Of all hemophilia cases, 80-85% are Hemophilia A, while Hemophilia B accounts for 14%.[9] The remainder of the hemophilia cases are due to other clotting abnormalities. As of today, there are only six cases (5 males and 1 female) of Hemophilia A recorded in our institution and our patient is the first and only case of Hemophilia B.

The genes involved in Hemophilia are located on the "X" chromosome, otherwise known as "sex" chromosome because it determines whether a person is a male or a female. Men have one X chromosome which they inherit from their mother and one Y chromosome which they inherit from their father. Women have two X chromosomes which they inherit from each parent. If the X chromosome a man inherits from his mother has the altered gene, he will have hemophilia. If a woman inherits a copy of the altered gene from either of her parents, she is said to "carry" the hemophilia gene and is therefore called "carrier". She has a normal and an altered copy of the gene.[8] (Figure 5)

All daughters of a father with hemophilia will inherit his altered copy of the X chromosome. None of the sons will be affected since they got their X chromosomes from their mother who has normal X chromosomes.[8] (Figure 5)

Carriers who have one normal and one altered gene have a 50% chance of transferring the altered gene to all their children. Boys who inherit the altered gene from their mother will have hemophilia, while girls who inherit the altered gene from their mother will be carriers.[8]

For many years, people believed that only men could have symptoms of hemophilia and women are just "carriers" and therefore do not experience symptoms. According to the World Federation of Hemophilia, a woman who has less than 40% of the normal level of clotting factor is no different from a man with the same factor level- **she has hemophilia**.[8] A woman with levels of 40-60% of the normal amount of clotting factors who experiences abnormal bleeding is called a symptomatic carrier.[8] Female carriers are expected to have 50% of the plasma concentration of factor VIII or IX found in healthy individuals and their factor level is generally sufficient for normal hemostasis. In female carriers, one of the two X

chromosomes is turned off, or "suppressed". This process is called "lyonization" after Mary Lyon, who first described it.[8] It is a random X-inactivation which takes place in the early embryonic life. If the chromosome that is turned off contains the altered gene, the female carrier may not manifest symptoms since the X chromosome that contain normal gene will produce the needed clotting factor.[8] If the X chromosome with the normal gene is the one that is "turned off", then the female carrier will not produce clotting factors or the clotting factors that are produced won't work properly.[8] The rarity of the latter event explains the low frequency of women with clinical hemophilia.[11]

There are two types of carriers namely: obligate and possible carrier. Obligate carriers are those that necessarily have the hemophilia gene which they inherit from their father. They can be identified by obtaining a detailed family history known as pedigree. Anyone of the following can be an obligate carrier: (1) all daughters of a father with hemophilia, (2) mothers of a son with hemophilia and who have at least one other family member with hemophilia (a brother, maternal grandfather, uncle, nephew or cousin), (3) mothers of one son with hemophilia and who have a family member who is a known carrier of the hemophilia gene (a mother, sister, maternal grandmother, aunt, niece or cousin) (4) mothers of two or more sons with hemophilia.[8] On the other hand, possible carriers are anyone of the following (1) all daughters of a carrier (2) mothers of one son with hemophilia but who do not have any other family members who have hemophilia (or are carriers) (3) sisters, mothers, maternal grandmothers, aunts, nieces and female cousins of carriers.[8]

The patient's mother is an obligate carrier since the maternal grandfather has hemophilia. Our patient has a maternal aunt who is also an obligate carrier and who bore a son who was diagnosed to have hemophilia B (Figure 2). Since the level of factor IX in our patient is low (1.6%-3.4% of normal) and comparable to the level of a male with hemophilia, we can consider our patient as a female with hemophilia rather than a symptomatic carrier. Since mutation analysis, which is confirmatory in detecting whether a patient is a carrier or not, is not available in our country, we have to make use of the pedigree analysis and factor IX assay test in the diagnosis of Hemophilia B in our patient. It is probable that the normal X chromosome in our patient has been inactivated through the process of lyonization, thereby resulting to a low level of factor IX in her blood. There are three conditions that can make a female manifests clinical bleeding due to hemophilia.[9] First is extreme lyonization (inactivation of the normal Factor IX allele in one of the X chromosomes). Second is homozygosity for the hemophilia gene (father with hemophilia and mother who is a carrier, two independent mutations, or some combination of inheritance and new mutations or (3) Turner syndrome (XO) associated with the affected hemophilia gene. The most probable condition that is applicable to our patient is the first. The father of our patient denies history of any bleeding tendency as well as history of any bleeding disorder in his family. Turner syndrome is not present in our patient.

Symptoms are quite variable, depending on the type and severity of hemophilia (Table 8) which in turn depends on the amount of clotting factor in the person's blood.[8,9,12] Mild hemophilia is when more than 5% but less than 40% (>0.05 - <0.40 IU/ml) of the normal amount of clotting factor is present. Moderate hemophilia is when 1-5% (0.01-0.05 IU/ml) of the normal amount is present. Severe hemophilia is when less than 1% (<0.01 IU/ml) of the normal amount of clotting factor is present in the patient's blood.

Table 8: Levels of Severity of Hemophilia [8]

Mild	more than 5 to 40% of the normal amount of clotting factor (>0.05- 40 IU/ml)
Moderate	1-5% of the normal amount of clotting factor (0.01-.05 IU/ml)
Severe	less than 1% of the normal amount of clotting factor (<0.01 IU/ml)

In 2004, Plug I, Mauser-Bunschoten E, et.al., did a large national cross-sectional genetic testing regarding bleeding in women in whom genetic testing for hemophilia was performed.[7] They focused on spontaneous bleeding events, bleeding after trauma and bleeding following surgical intervention. They did not distinguish between the 2 types of hemophilia in their study. They included 519 women, 274 was carrier and 245 were non carrier. They concluded that women with mildly reduced clotting factor levels (between 0.41 and 0.60 IU/ml) may have bleeding manifestation similar to those women with very low level of clotting factors, but they differ in the frequency and severity of bleeding.

Symptomatic carriers and women with Hemophilia may bruise more easily. They may experience prolonged bleeding after surgery or trauma. The most common symptom women experience is prolonged bleeding after tooth extraction.[8] When our patient had tooth extraction when she was 4 years-old, it took seven days for the gum bleeding to stop. She had hematoma due to tetanus vaccination when she was 6 years-old. She had history of epistaxis upon waking up when she was 9 years-old. They often have heavier and more prolonged bleeding during their monthly periods and are more likely to require iron

supplement or undergo hysterectomy. Our patient used to have regular monthly periods of normal amount and duration until nine weeks prior to admission when she was admitted because of profuse vaginal bleeding. Carriers and female with hemophilia have a greater risk of heavy or prolonged menstrual period.[8] The profuse vaginal bleeding found in our patient is due to the low level of factor IX present in her blood (1.6 to 3.4% of the normal).

The hallmark of hemophilia is hemorrhage into the joints (hemarthrosis).[9] The place where 2 bones meet is called a joint. The ends of bones are covered with a smooth surface called cartilage. The bones are partly held together by a joint capsule that has a lining called synovium which has many capillaries. The synovium makes a slippery, oily fluid that helps the joint moves easily (Figure 6). When the capillaries in the synovium are injured, they may bleed. Usually, there is no cause for the bleeding, especially in those with severe hemophilia. In a person who does not have hemophilia, the normal level of clotting factors in the blood is enough to stop the bleeding. However, in a person with hemophilia, the bleeding continues and causes the joint to swell, becomes painful and hard to move.[5] Those with hemophilia know when the joint starts to bleed because there will be tingling sensation and the joint will feel warm (Figure 8).[5] The most common "joint bleeds" happen in the ankles, knees and elbows (Figure 7).[5] Bleeds into other joints like the toes, shoulders, and hips can also occur (Figure 7).[5] Joints of the hands are not usually affected except after injury. Repeated bleeding into the joints may result in permanent deformities, misalignments, loss of mobility and extremities of unequal lengths (Figure 9).[5] When our patient was eleven years and six months old, she was admitted due to swelling and pain on her right elbow and left knee. She was then transfused with eight units of Fresh Frozen Plasma. She was again admitted when she was thirteen years old, because of swelling and pain of her left upper and left lower extremities including the left elbow and left knee. Four units of Cryosupernate were transfused. Luckily, there was no recurrence of the above mentioned symptoms.

Women with bleeding disorders are more likely to experience pain during their menstrual period. They may also experience a small amount of interval bleeding during ovulation which may cause abdominal as well as pelvic pain. The interval bleeding due to ovulation may be severe in carriers with very low clotting factor level.[8] Fortunately, our patient does not complain of dysmenorrhea or mid-cycle pain despite of her low factor IX level.

During the process of anovulation, women can develop simple or functional ovarian cyst that can developed into a hemorrhagic ovarian cyst in women who are carriers and women with hemophilia.[8] Hemorrhagic

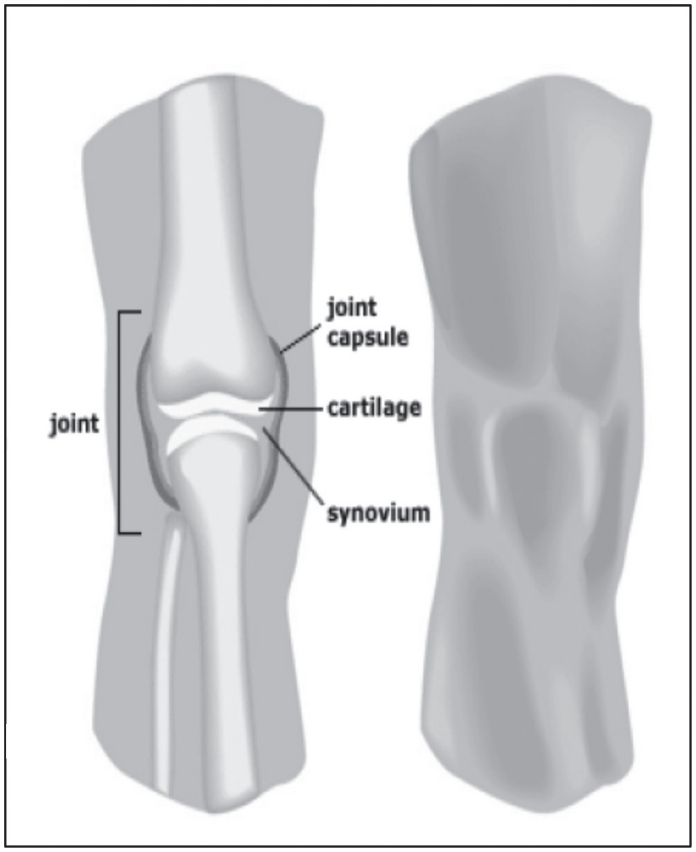


Figure 6. Anatomy of a joint[5]

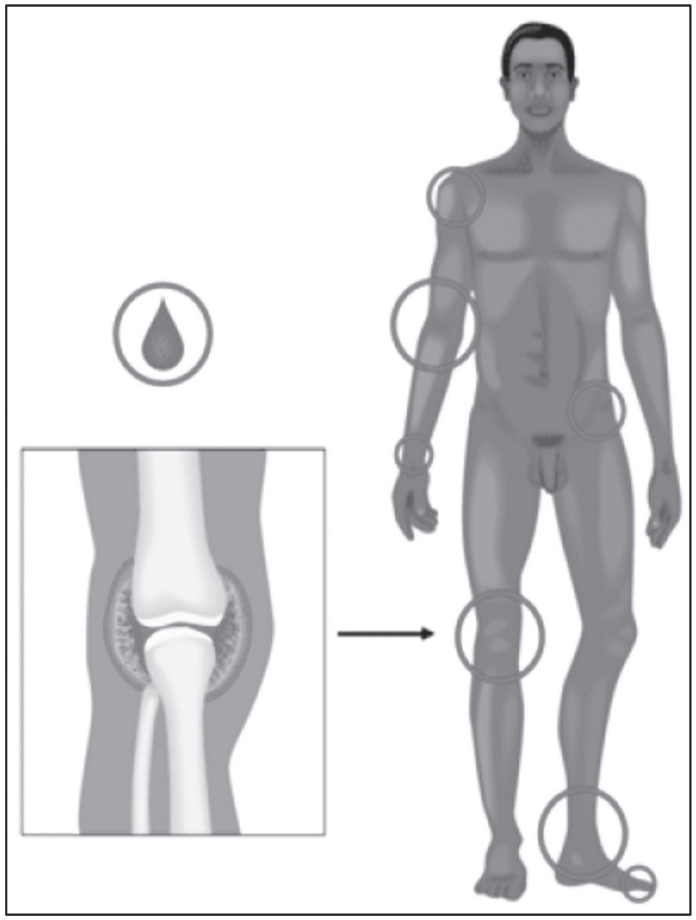


Figure 7. Common sites of "joint bleeds" [5]

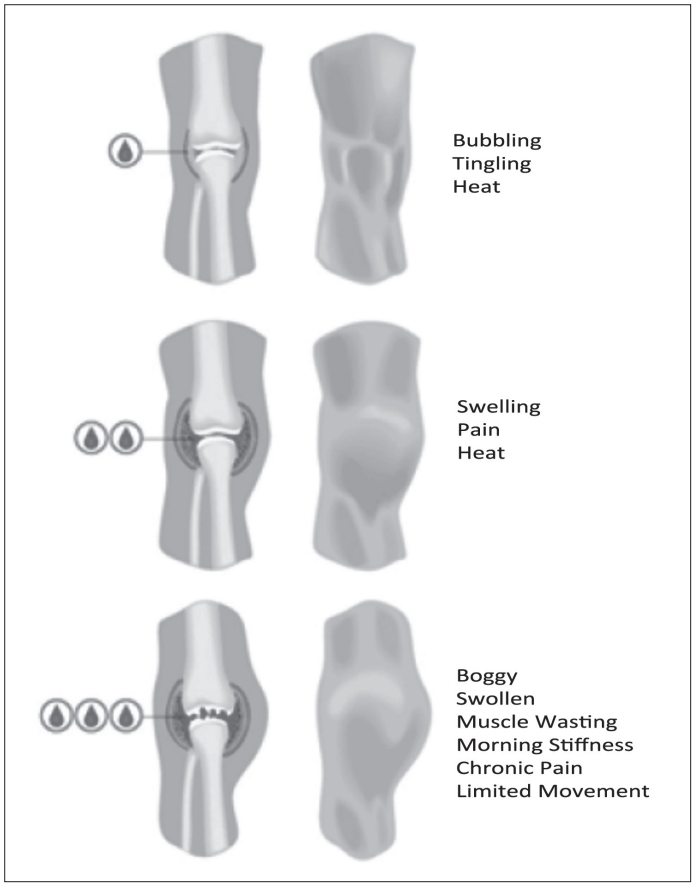


Figure 8. Signs and symtoms of "joint bleeds" [5]

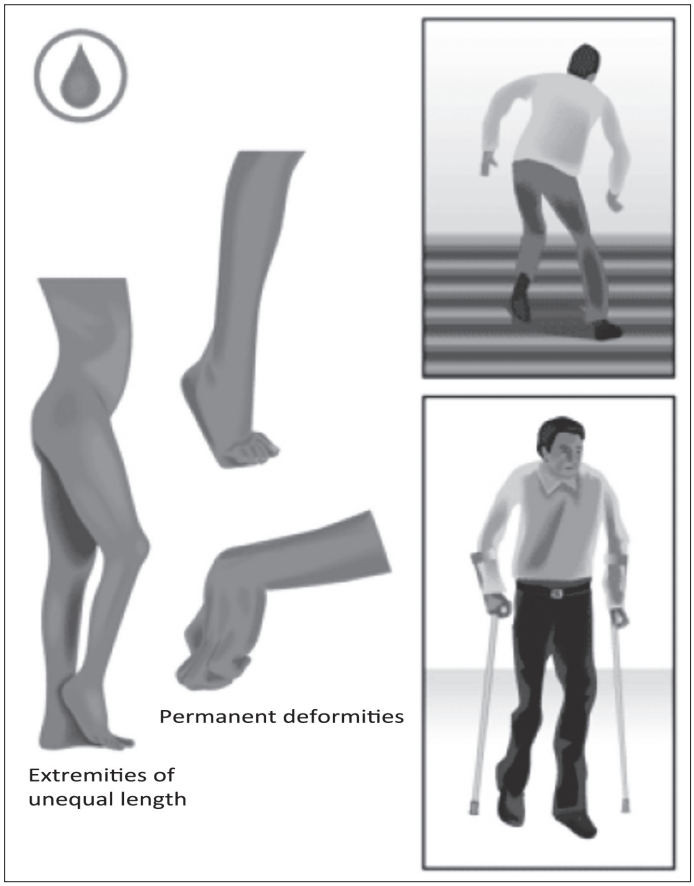


Figure 9. Long term effects of joint bleeds and muscle bleeds[5]

ovarian cysts can cause considerable pain. Transrectal ultrasound done in our patient during her last admission showed normal ovaries.

A high index of suspicion for a possible bleeding abnormality should be maintained in all patients who present with excessive bleeding since the prevalence of uterine abnormalities in patients with bleeding disorders is uncertain. A complete history and physical examination should be obtained. In adolescence, intrauterine pathology is rare and an unlikely cause of heavy menses.[6] An in-depth coagulation investigation should be considered as part of the initial assessment even in the absence of a pelvic examination. Pelvic examination is not mandatory and can be done at the discretion of the gynecologist.[13] Initial testing should include a platelet count, hemoglobin/ hematocrit, ferritin, prothrombin time and activated partial thromboplastin time.[6] Our patient had normal platelet count and prothrombin time but prolonged activated partial thromboplastin time. Factor VIII assay test showed normal level but Factor IX level was low. Ferritin level determination was not done in our patient.

Diagnosis of carriership of hemophilia is based on DNA analysis, pedigree analysis, or the assessment of clotting factor levels.[7] Since DNA analysis is not available in our country, the diagnosis of our patient was made on the basis of the pedigree analysis and low level of factor IX. The pedigree analysis will clearly show that the patient is a possible carrier but the very low level of factor IX in her blood made the hematologist classify her as a female with Hemophilia B of moderate severity.

Genetic test, specifically mutation analysis looks directly for the altered gene that is responsible for hemophilia.[8] It is the only way to be absolutely sure that a woman is a carrier.[8] Factor levels vary significantly among family members, therefore each known or suspected carrier within a family should have factor assay test. Factor levels alone cannot confirm a woman's carrier state.[8]

There are several strategies or options that are available for the treatment of abnormal bleeding in women with inherited bleeding disorder like hemophilia. They can be divided into two categories, medical or surgical. Management should be individualized and best undertaken jointly by a gynecologist and a hematologist. Medical therapies can be divided into hormonal treatments, non-hormonal treatments and blood products.[6] Surgical therapies comprise of endometrial ablation and hysterectomy.[6]

Hormonal therapy is usually the first line of therapy in women with inherited bleeding disorders.[6] They are safe for use in adolescents with no adverse effect on their future fertility or attainment of peak bone mass.[13] Combined oral contraceptives reduce menstrual blood loss

by approximately 50%. The monophasic pill (containing 30-35mcg of Ethinyl estradiol) taken in a continuous non-stop regimen may be given to women with anemia or in those who experience a hemodynamic challenge during menses.[6] Breakthrough bleeding can be treated by doubling in the combined oral contraceptive pills for 3 to 4 days or by applying a 50 mcg transdermal estrogen patch for 3-4 days. If the breakthrough bleeding persist, a 50 mcg combined oral contraceptive pill could be used instead. If there is heavier or active bleeding, an oral contraceptive pill (OCP) taper regimen can be used. A common approach is to give one pill four-times daily until bleeding stops then one pill three times for 3 days, then one pill twice daily for 2 days followed by one pill once daily.[1] After completing the OCP taper, the patient can continue taking OCP monthly. Our patient was given combined oral contraceptive pill which was given as follows: 1 tablet every 6 hours for 4 days, 1 tablet every 8 hours for 3 days, 1 tablet every 12 hours for 2 days, 1 tablet once a day for 21 days. Combined oral contraceptive pills are usually use in combination with Tranexamic acid during scheduled bleeding. Because oral contraceptive pills suppresses ovulation one of its added benefit is it helps prevent ovulation bleeding in female with bleeding disorders.[13]

Another hormonal agent that can be given to those with inherited bleeding disorder is Depot Medroxyprogesterone Acetate (DMPA). It is given as an intramuscular injection once every 3 months but if given, pressure should be applied to the injection site for 15 minutes.[6] In the case of our patient, it is better not to give intramuscular injection since her factor IX level is quite low. She already had history of hematoma formation in her deltoid due to tetanus vaccination. She was also given Medroxyprogesterone acetate when she first consulted her attending gynecologist. Her vaginal bleeding stopped but the withdrawal bleeding became profuse which made the patient seek admission.

Levonorgestrel-releasing intrauterine system (Mirena IUS) can also be used to control heavy menses in patients with inherited bleeding disorder. Mirena releases 20 micrograms of levonorgestrel per day which effectively suppress endometrial growth and reduce menstrual blood loss by 74 to 97%.[6] Its use is not usually considered in adolescent because of the lack of data about its acceptability and safety in these age group. There is also a potential risk of pelvic inflammatory disease as well as difficulty of inserting the device.[13]

Danazol and gonadotrophin-releasing hormone analogs can be used to effect endometrial thinning.[6] Oligo/amenorrhea can be induced with a dose of 100-200 mg per day given over a period of 3 months.[6] The maintenance dose is 100 mg per day or 100 mg per day every other day. The GnRH induced hypoestrogenism results in thinning of the endometrium until the patient becomes amenorrheic. GnRH analogs are not usually given due to its significant side effects including bone loss and menopausal symptoms such as hot flushes and vaginal dryness. Danazol and GnRH analogs are both not appropriate for our young patient.

Non hormonal treatments include antifibrinolytic agents and iron supplements. The antifibrinolytic drug Tranexamic acid substantially reduces the fibrinolytic capacity of menstrual blood and stabilizes the clot.[6] It decreases blood loss by 50%. Its main advantage is that it may be taken only during the menstrual period. The standard adult dose of Tranexamic acid is one gram per orem every 6 hours.[6] It can be given intravenously (10mg/kg every 6 hours). Initially, Tranexamic acid was given intravenously to our patient. It was later shifted to oral after a decrease in the amount of bleeding was noted. Iron replacement therapy should be given to women with anemia. Our patient was given iron preparation since her complete blood count showed anemia on admission.

Blood products may be given to women with inherited bleeding disorders.[6] Our patient is transfused with three units of packed RBC which are enough to bring her hemoglobin and hematocrit to normal levels. There is no need to give Fresh Frozen Plasma or Cryosupernate since the vaginal bleeding stops just by using combined oral contraceptive pills and tranexamic acid. Factor IX assay test shows a higher level (3.4% of normal) compared to the levels during her two previous admissions (1.6% and 2.4 % of normal). Factor IX concentrate is not available locally. Fresh Frozen Plasma (FFP) and Cryosupernate were given to our patient during her previous admissions. Cryosupernate is the product that remains when Fresh Frozen Plasma is processed to make Cryoprecipitate. It contains plasma proteins and all of the other clotting factors (including II, VII, IX and X). It can be used for all of the same indications as FFP except for Hemophilia A and Von Willebrand's Disease. It is particularly useful for coagulopathies such as Hemophilia B (Factor IX deficiency) and warfarin poisoning. Fresh Frozen Plasma is the liquid portion of human blood that has been frozen and preserved after a blood donation and will be used for blood transfusion. It is effective in the treatment of deficiencies of factors II, V, VII, IX, X and XI when specific component therapy is not available.

The formation of alloantibodies to factor IX is a major complication in the management of Hemophilia B. Some people with Hemophilia develop antibodies called inhibitors after they have received factor concentrate. An inhibitor can develop only after a person with congenital hemophilia has been treated with replacement clotting factor. Inhibitor formation is more common when you use factor concentrate than fresh frozen plasma in the

treatment of hemophilia. Inhibitors to factor IX are detected in only 3-5% of all Hemophilia B patients as compared to the prevalence of inhibitor to factor VIII which is about 5-10% of all cases and approximately 20% of severe Hemophilia A patients.[12] The high risk group for inhibitor formation includes those with severe deficiency (>80% of all cases of inhibitors), familial history of inhibitors, African descent, mutations in the factor VIII or factor IX gene resulting in deletion of large coding regions, or gross gene rearrangements. [12] The presence of inhibitors should be suspected when patients do not respond to factor replacement at therapeutic doses. The laboratory test required to confirm the presence of an inhibitor is an aPTT mixed with normal plasma. In most hemophilia patient, a 1:1 mix with normal plasma completely corrects the aPTT. In patients with inhibitors, the aPTT on a 1:1 mix is abnormally prolonged, because the inhibitor neutralizes the factor IX clotting activity of the normal plasma.[12] The most effective strategy of eradicating inhibitor antibody is immune tolerance induction (ITI). Daily infusion of the missing protein should be given until the inhibitor disappears. This usually takes more than one year with success rate in the range of 60%.

Surgical options available for carriers and female with hemophilia include endometrial ablation and hysterectomy.[6,8] In endometrial ablation, the endometrium is permanently destroyed and is not recommended for women who want to have children. Hysterectomy is the removal of uterus. This can be done in women who do not wish to get pregnant. These two options were not considered since our patient was only an adolescent.

Ideally our patient and her family should be referred to a geneticist for counseling. Because of the very young age of our patient, the attending gynecologist opted to delay the referral until the patient is old enough to understand everything regarding her condition. She however explained to the patient and her family the basic information which they should know about Hemophilia B. They were informed of the possibility of transmitting the hemophilia gene to our patient's children.

Pregnancy is not contraindicated in patients with coagulation disorder but it requires a multidisciplinary approach to management between the obstetrician, hematologist, anesthesiologist and pediatrician. They should be seen by the obstetrician as soon as they suspect they are pregnant. They should be given the best care during pregnancy and childbirth and potential complications for the mother and the newborn should be minimized.

Some people simply accept the possibility of having an affected child. Others choose to adopt a child or to use other conception options like in vitro fertilization (IVF) with post implantation diagnosis, IVF with egg donation and sperm sorting (Table 9).[8] A definitive prenatal diagnosis of whether a child is affected or not can be made through amniocentesis or chorionic villus sampling8 but they are only of use in countries where abortion is legal. In X-linked diseases like hemophilia, determining the sex of the baby by ultrasound is recommended since the information will be useful during the time of delivery. The risk of miscarriage in carriers of hemophilia does not appear to be increased.[8]

In preparation for delivery, factor levels should be measured during the third trimester.[6,8] Factor IX levels usually do not change significantly during pregnancy. After delivery, factor levels usually return to baseline levels in 7-10 days but sometimes the decrease occur earlier. An inherited bleeding disorder is not an indication for delivery by Cesarean Section. The decision to do a Cesarean Section should be based on obstetrical indication.[6] The delivery should be as atraumatic as possible and prolonged labor should be avoided. Vacuum extraction and forceps should not be used.[6,8]

The risks of early postpartum hemorrhage (during the first 24 hours after delivery), among women with inherited bleeding disorders is increased to 16-22% as compared to the general population which is 4-5%.[6] The risks of late postpartum hemorrhage is also increased to 11-24% as compared to less than 1% in the general population.[6] Those who are at risk for late postpartum hemorrhage should have their hemoglobin levels checked before discharge. Epidural and spinal anesthesia are contraindicated.[6] There is no contraindication to regional anesthesia if coagulation is normalized. If the baby is at risk of having a bleeding disorder, blood samples of cord blood should be taken to determine the factor level in the newborn.[6,8] Intramuscular injection and circumcision should be avoided until adequate work ups are done and the results of blood tests of the newborn are known.[6,8]

Being diagnosed with hemophilia B can have an impact on patient's quality of life. Her self-image and confidence can be negatively affected if she experiences embarrassment because of heavy menstrual bleeding which results to her school uniform having blood stain. She needs to avoid any "contact" sports or trauma and this may prove difficult for her since she cannot join her friends in certain activities. She may feel that she should not get married and have children because of the possibility of passing on the bleeding disorder. All the professionals taking care of the patient should provide information and moral support to help her understand better her condition.

SUMMARY AND CONCLUSION

Coagulation disorder is the second most common cause of heavy menstrual bleeding during adolescence. An inherited bleeding disorder should be suspected if

Table 9. Conception options for carriers of hemophilia[8]

Procedure	How it's done	Things to consider
In-vitro fertilization (IVF) with pre-implantation diagnosis (PGD)	The woman's eggs are retrieved and fertilized in the laboratory with the sperm from the woman's partner. This is called in-vitro fertilization (IVF). When the embryos are at a very early stage of development, a test is done to determine whether they carry the altered hemophilia gene. Only those that do not contain the altered gene are implanted into the mother's womb.	This procedure is expensive and not available in many parts of the world. The success rate for a pregnancy with IVF is approximately 30 per cent per cycle. CVS or amniocentesis is still recommended to confirm that the fetus does not carry the altered gene.
IVF with egg donation	Using donor eggs from a fertile woman who is not a carrier of hemophilia ensures that the child would not be at risk of inheriting the hemophilia gene from the mother.	Again, IVF is expensive, with a success rate for pregnancy of approximately 30 per cent per cycle. The success rate is best when the donor is young.
Sperm sorting	Only sperm carrying an X chromosome is used. This ensures the birth of a female child.	The female child may still inherit the altered gene and be a carrier of hemophilia. She could experience bleeding symptoms and may pass the altered gene on to her children. This method is only available in specialized centres as a research tool and it is till under evaluation.

Source: Adapted from All About Carriers, Canadian Hemophilia Society

there is a personal and family history of bleeding.

We presented a 13 year old female with heavy menstrual bleeding and a family history of Hemophilia B. Hemophilia B is an X-linked hereditary bleeding disorder caused by a deficient or defective coagulation factor IX. Due to its recessive X-chromosomal inheritance pattern, mostly males are affected and females are usually "carrier" of the hemophilia gene and are generally asymptomatic. Carriers has one X-chromosome with normal gene and one X-chromosome with altered gene. Through a rare event called "lyonization" which is a random process, the X-chromosome with the normal gene may be inactivated or suppressed thereby resulting to a low factor IX level which is comparable to the factor level of a male with hemophilia B. These female with hemophilia B usually presents with bleeding manifestations especially heavy menstrual bleeding.

Diagnosis of carriership of hemophilia was based on DNA analysis, pedigree analysis, or the assessment of clotting factor levels. DNA analysis is not available in our country, hence the basis for our diagnosis in our patient are the pedigree analysis and results of Factor IX assay tests done which showed levels of <5% of the normal. Based on her factor IX levels, she has moderate hemophilia B.

Treatment of heavy menstrual bleeding in women with inherited bleeding disorders should be individualized. Management options can be medical or surgical. Hormonal therapy is usually the first line of therapy even in an adolescent. Medical management can be hormonal, non-hormonal or blood products. Since our patient is an adolescent, surgical options are not considered.

A multidisciplinary approach with involvement of a gynecologist and a hematologist would be beneficial in the management of our patient. Genetic counseling should be offered when she reaches the appropriate age to make her understand her condition especially if she has plans of having a family in the future.

Pregnancy is not contraindicated in patients with coagulation disorder but it requires a multidisciplinary approach to management between the obstetrician, hematologist, anesthesiologist and pediatrician so that potential complications for the mother and the newborn could be minimized.

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