

## A WOMAN WITH SPORADIC HEMOPHILIA-B DIE BECAUSE OF CEREBRAL BLEEDING: A Rare Case in Bali-Indonesia

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**Background:** Hemophilias are groups of blood clotting disorder caused by deficiency of blood clotting factors which is X-linked recessively inherited and explain why mostly man is the affected victim. But on an extremely rare condition a women can have hemophilia due to several reasons and sporadic hemophilia is used to describe when hemophilia appeared without ascent and decent history of hemophilia. A 38 years old women with a peripheral spontaneous bleeding for two days although an open flap and a cauterization to stop the bleeding has been applied. She was the third child of 7 children in the family, 3 of them were man with normal life and 4 women also have no history of bleeding. Her parent and grand-parent were all dead because of aging problems. She also has 2 sons with ages of 10 and 13 years, respectively, live normally. **Results:** factor VIII activity 192 seconds (control: 80 seconds), factor IX activity 2 seconds (control: 111 seconds), hence patient was considered suffered from sporadic haemophilia-B due to low level of factor IX 1.8% and bleeding episodes mimicking clinical presentation of classical hemophilia patients while no known history of having hemophiliac family. The different diagnose were Von Willebrand Disease (VWD), symptomatic carriers, acquired hemophilia. After several admissions and repeatedly bleeding episodes patient died because of intra cerebral bleeding.

**Keywords:** hemophilia-B; sporadic hemophilia; cerebral; bleeding.

### INTRODUCTION

Hemophilias are groups of blood clotting disorder caused by deficiency of a blood clotting factors which is X-linked recessively inherited and explain why mostly man is the affected victim. According to World Foundation of Haemophilia (WFH) reported that hemophilia affect 400.000 patients globally where hemophilia-A almost four times as much as hemophilia-B. Hemophilia-A having factor VIII deficiency while hemophilia-B (also known as Christmas disease) caused by factor-IX deficiency. The disease is not influenced by race, geography and socio-economic conditions.<sup>1-4</sup> Besides congenital hemophilia which is transmitted through generation, hemophilia can also be acquired later in life called acquired hemophilia where bodies produce antibodies to inhibit coagulation factor to normally function. The incidence of hemophilia B is estimated at 1:30.000 live-born men. These hemophilias affect most

exclusively male with defective gene that located on X-chromosome and transmitted a normal Y chromosome to all his son but an abnormal X chromosome to all his daughter, his son will not be affected and all of his daughter will be a carriers. But on an extremely rare condition a women can have hemophilia due to several reasons such as having two mutant gene from hemophilic father and carrier mother, one gene mutation with lyonization (extreme non-random X chromosome inactivation), spontaneous gene mutation (somatic and germ-line mutation). When hemophilia appeared without ascent and decent history of hemophilia, therefore, sporadic hemophilia is used to describe them, whereas isolated case is addressed if a single boy is born in family with no history of hemophilia and sporadic sib-ships when his brother also having hemophilia.<sup>5-7</sup>

Hemophilia in women is extremely rare. Reports in 1978 from 11 hemophilic centers showed that women with hemophilia-A was found 10 and hemophilia-B in 6 women.<sup>7</sup> In general hemophilia-B is more common than hemophilia-A. There were 895 hemophiliac patients scattered in 21 provinces with the national prevalence of hemophilia estimated to be 4.1 per 1 million population according to Indonesian Reports in 2005. Numbers are gets increase and reached 1388 in year of 2011.<sup>9</sup>

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Male (XhY) is a patient with clinical manifestation of bleeding while women (XXh) usually only as a carrier. Women carrier of hemophilia usually is asymptomatic. But some woman with carrier of hemophilia may experience bleeding and called as a symptomatic carrier. Approximately 30% of female carrier of hemophilia has the activity of factor IX is lower than 30% of normal limits and can be categorized half hemophilia.<sup>10-13</sup> Manifestations of bleeding may also occur in women when accompanied by chromosomal abnormalities eg. Gene mosaicism (46, XhX/XhO), Turner syndrome (XhO) or double heterozygote (XhXh) which is a condition in which the patient's father was a carrier of hemophilia and the mother is carrier but it is very rare.<sup>7</sup>

Hemophilia patients are characterized by frequent bleeding episodes due to ineffectiveness of their factor VIII or IX. Bleeding manifestations vary from mild, moderate or severe depending on the degree of hemophilia. Spontaneous bleeding occur mainly joint bleeding (hemarthrosis). Other symptoms are bleeding during tooth extraction, hematoma subcutaneous/intramuscular, oral mucosal bleeding, intracranial bleeding, retroperitoneal bleeding and retro-faringeal, epistaxis and hematuria. If cerebral bleeding occurred, it can be fatal and is the leading cause of death in hemophilia. Although more frequent in younger age, a significant number of cerebral bleeding also happened in adults.<sup>14</sup>

We therefore reporting the case of a woman with sporadic hemophilia-B with differentiated diagnosis von Willebrand Disease, acquired hemophilia and symptomatic carrier, suffered from repeatedly bleeding episodes then finally die because of intra cerebral bleeding.

#### **CASE**

A 38 years old women was consulted by Oral Surgery Departement to Hematology Division, Internal Medicine Deptatment with a peripheral spontaneous bleeding. Bleeding was continuous for two days although an open flap and a cauterization to stop the bleeding has been done. There was also a history of prolonged bleeding after a tooth extraction procedure two years before. She was the third child of 7 children in the family, 3 of them were man with normal life and 4 women also have no history of bleeding. Her parent and grandparent were all dead because of aging problems. She also has 2 sons 10 and 13 years of age, respectively live normally.

On admission her blood pressure was 120/80 mmHg, heart rate 96 times/min, respiration rate 18 times/min, body temperature 36°C, body weight 60 kg, 160 centimetres of height, and generally in a moderate condition. There was gum haematome and an active minor bleeding although an

adrenaline tampon were applied. No other significant findings on physical examination.

Laboratory findings on the blood sample were as follows: leucocyte 12,5 K/uL (normal: 4,5-11 K/uL), haemoglobin 9,6 g/dL (normal: 12-16 g/dL), haematocrite 21,2% (normal: 36-46%), MCV 88,6 fl (normal: 80-94 fl), MCH 31,5 pg (normal: 27-32 pg), thrombocyte 258 K/uL (normal: 150-440 K/uL). Bleeding time (Duke) 2 minutes 30 seconds (normal: 1-3 minutes), clotting time (Lee & White) 10 minutes (normal: 5-15 minutes), prothrombine time (PT) unread/error (control: 10.80 seconds), APTT 204.80 second (control: 36.5 seconds). The microscopic examination of peripheral blood smear suggested a normochromic anaemia and leucocytosis, based on normochrome anisocytosis on the red cells, relative increasing of leucocyte and differentiated neutrophilia, and a normal population of thrombocytes. Liver and kidney function test were within normal limits. While waiting further test to come patients was transfused with fresh frozen plasma. Gum bleeding is subsiding in the fourth day of hospitalization. The result of Coomb's test was A type of blood with Rhesus (D+), absence of coating for Auto Immune Antibody on the red cells in vivo (DCT negative) and negative free irregular Allo Antibody in the serum (ICT negative). The total billirubine level were 0.417 mg/dL and the indirect billirubine level were 0.28 mg/dL. In the ninth day, there was improvements of the patient's conditions and laboratory examinations were as follows: prothrombine time (PT) 19.7 second (control: 12.3 seconds), APTT 55.8 seconds (control: 35.8 seconds) and the INR points were at 1.69. The patient were temporarily discharged while waited for the examination results of factor VIII and IX. No other test such as mixing plasma test, DNA analysis etc can be done due to lack of facilities.

One week after the discharge, she was hospitalized again with another gum bleeding. With the results of factor level activity available which was factor VIII 192 seconds (control: 80 seconds), factor IX 2 seconds (control: 111 seconds), hence patient was considered suffered from sporadic haemophilia-B due to low level of factor IX 1.8% and bleeding episodes mimicking clinical presentation of classical hemophilia patients while no known history of having hemophilic family. The different diagnose were Von Willebrand Disease (VWD), symptomatic carriers, acquired hemophilia. Because of financial problems recombinant factor IX was unaffordable, fresh frozen plasma is the only modality to be given.

Gum bleeding was still occurred in the fourth day of treatment. The laboratory findings were as follows: AST 26.62 mg/dL (normal: 14-50 mg/dL), ALT 37.29mg/dL (normal:11-64 mg/dL), albumin 4.18 g/dL (normal 4.0-5.7 mg/dL), urea serum

3.513 mg/dL (normal: 6.0-22.0 mg/dL), creatinine serum 0.479 mg/dL (normal: 0.50-1.20 mg/dL), blood glucose 91.81 mg/dL (normal: 70.11 mg/dL), natrium 139.5 mmol/L, kalium 3.541 mmol/L, Prothrombin Time 22.7 seconds, APTT 59.0 seconds (control: 34 sec), INR 1.99. She was discharged after improvement of her condition. Nonetheless she had been hospitalized for many episodes of hospitalization because of repeatedly bleed and finally died due to cerebral bleeding.

## DISCUSSION

The hemostasis process initiated, promoted and progressed until stable thrombus is made to seal the injured vessel. In the coagulation cascade, *prothrombin* activator could be formed by extrinsic and intrinsic pathway. Factor IX plays a role in the intrinsic pathway. The activated factor IX, activated factor VIII and thrombocyte phospholipid would activate factor X. The chain reactions continued with activated factor X bonding to tissue phospholipid and factor V formed prothrombin activator, which is transform prothrombin to thrombin. From the coagulation cascade, it showed that inadequacy of factor IX would disturb the hemostasis process as shown at Figure 1.<sup>1</sup>

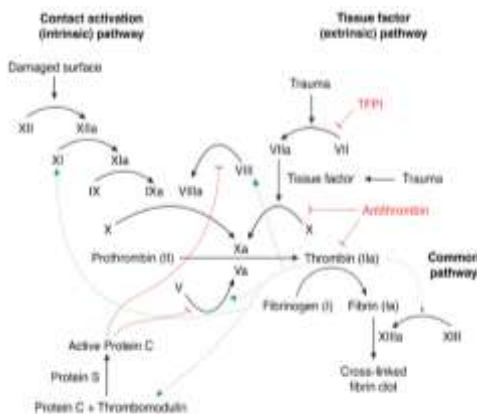


Figure 1  
 Coagulation cascade

The diagnosis of hemophilia B (inherited factor IX deficiency) requires confirmation of a factor IX activity level below 40 percent of normal or a pathogenic factor IX gene mutation.<sup>15</sup> Diagnosis of Hemophilia B in this patient was supported by history of repeatedly bleeding episodes, prolonged APTT value: 204.80 seconds (control 36.5 seconds), and the shortened of factor IX: 2 seconds (control: 111 seconds) (1.8%). Severity of type B hemophilia depends on the activity of factor IX. The normal range is around 0.5-1.5 U/dL (50-150%). It is severe hemophilia if the level is < 1% of factor IX, moderate has a level of 1-5%, and the mild stage if activity level > 5-30%. A spontaneous

bleeding were rarely happen in the mild stage hemophilia, mostly happened in the moderate-severe stage of hemophilic.<sup>1,3,4</sup> In the mild form of hemophilia, bleeding manifestation appeared after a traumatic event or post operation procedure. As in our case, she finally died because of cerebral bleeding that occurs spontaneously after several episodes of bleeding. Her factor IX activity is only 1.8% considered in moderately high severity. Spontaneous intracranial bleeding is the common cause of death in a severe hemophilia. A study in Argentina indicates that 7.5% of hemophilic patients suffered intracranial bleeding in the average age around 14.8 year, and 72% manifested in less than 20 years old.<sup>14-16</sup> Cerebral bleeding is more prevalence in younger age, although a significant numbers of cerebral bleeding also occurred in aging, suggested that other risk factors such as hypertension is increasing as hemophilic patient gets older.

The chance to have cerebral bleeding increased when hemophilia is severe inhibitor is high hypertension and thrombocytopenia.<sup>14</sup> Inheritance patterns of B type hemophilic is passed recessively in the X chromosome, and females could only be a carrier because she only has one abnormal X chromosome that inherited from a hemophilic father or a carrier mother.<sup>17-19</sup> However, certain conditions having abnormality of both X chromosome, homozygosity of locus deformity, and a lyonization (inactivation) process a female subject could suffered recessive X linked chromosome diseases (hemophilia). As shown at Table 1, some causes or etiologies of women with hemophilia.<sup>7</sup>

Table 1  
 Etiology of Female Hemophilia

### Two gene mutation

- Father with hemophilia father and mother is a carrier.
- Father with hemophilia and mother with new mutation of X chromosome.
- Mother is a carrier but father with new mutation of X chromosome.
- Both father and mother with germ-line new mutation of their X chromosome

### One gene mutation with non random or extreme inactivation (*lyonization*) of X chromosome

#### One gene mutation on XY genotype phenotypically as women

#### Abnormal X chromosome with

- Deletion on one of the normal X chromosome.
- Deletion on half of the normal X chromosome

Carrier with lyonization caused her factor IX activity low increased, their risk of bleeding manifestation. On average, less than 30% carrier females had the lyonization process. A study in Netherland in 2006, has shown that the risk of prolonged bleeding time (more than 5 minutes) from small wound and the post operation bleeding time two folds on the carriers, compared to those who are not carriers from the same family.<sup>19-20</sup> An analysis of two females suffered from type A hemophilia in 1989 and 2008, her mother were carrier and normal father by the Restriction Fragment Length Polymorphisms (RFLPs) analysis indicated that there were extreme differentiation of hybridization fragment and an extreme non random inactivation of X chromosome that causes type A hemophilia in those females.<sup>21-22</sup>

As in our case, another explanation might be our patient is a carrier with lyonization (non-random inactivation of normal X chromosome) which made her having moderat-severe state of hemophilia. But carrier in our case has not been proven because her father was not hemophilic patient. The right way to confirm a woman is a carrier is to check her DNA mutation and found similarity between patient and their affective relatives. And also carrier usually has mild phenotypic expression of the disease.<sup>23</sup> There are two types of hemophilic genetical analysis procedures, which is probing a marker of of destructed factor IX in the familial X chromosome (linkage analysis), and direct mutation etiology identification of factor IX (direct mutation detection). The type of mutation could be a deletion, insertion, point mutation, missense mutation, nonsense mutation, and split slice mutation.<sup>1,5,7</sup> The examination of genetic mutation has not been done in this case.

Based on the explanation available we strongly suggest our case is sporadic hemophilia B because no known history of hemophilia running in the family neither ascendant nor decendent and sporadic hemophilia tends to have a moderate untill severe hemophilia.<sup>1,3,7</sup> Most of them are new gene mutations and inherited to the next generations as a female carriers without any male hemophilic, especially in the small sized families.<sup>5,7</sup> Environmental factors were suspected as the cause of the sporadic hemophilia. Observation of de novo gene mutation showed that the mutation has been started from embryogenesis stage not only single germ cell but also germ line mosaicism or somatic mosaicism. Somatic mosaicism is a genetical difference that happened in somatic tissue or germ-line, which affected at least two derivates cells from the same zygote. If mosaicism only happened in somatic cell population, the phenotype is affected depend on the population of mosaic cell population and not continuously derivate the genotype mosaic.

If the mutation affected the organ that produce factor IX with the somatic mosaicism such as the liver, the manifestation of the bleeding will be appeared. Subjects with the mutation that happened in testis or ovary will not affected the individual, but it will affected their descendants as a hemophilic or carriers, as shown in Figure 2.<sup>7,24-25</sup>

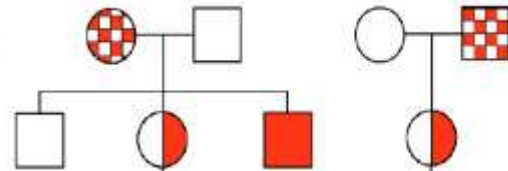


Figure 2

Mutation (*somatic+germ line mosaicism*) that happened to the embryo which is view cell and ovum or sperm, shown a phenotype affected depends on the population of mosaic cell, but it will affected their descendants as a hemophilic or carriers.

Other etiologies assumption were a new mutation of germ cell on both parents, a new mutation of germ cell on one of the parent (ovum or sperm) with non random or extreme inactivation (lyonization) of normal X chromosome, a mutation of female hemophilic zygote (at the early stage of embryogenesis) with non random or extreme inactivation of normal X chromosome, or a mosaic deletion of X chromosome, karyotype 46XX, 45XO and most of tissue that produce factor IX (45XO). Figure 3-8 showed few examples of probability diagram of female hemophilic.<sup>7</sup>

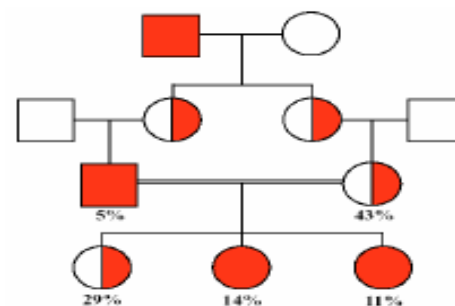


Figure 3

A female hemophilic caused by homozygote, with a hemophilic father and a carrier mother.

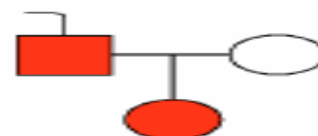


Figure 4

A female hemophilic caused by inherited X chromosome of hemophilic father with inactivation of X chromosome that i herited from the mother.

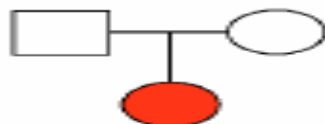


Figure 5

A female hemophiliac caused by a new mutation on X chromosome of both parents or one of them with inactivation of normal X chromosome.

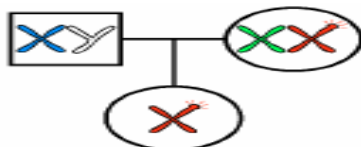


Figure 6

A female hemophiliac mutation of X chromosome (*caryotype* 45X0: syndrome Turner's) caused by a normal X chromosome deletion.

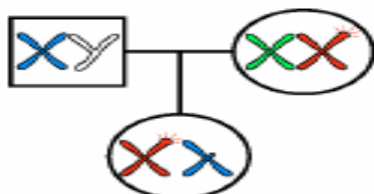


Figure 7

A female hemophiliac caused by deletion of some X chromosome with normal factor IX and the other X chromosome has been mutated.

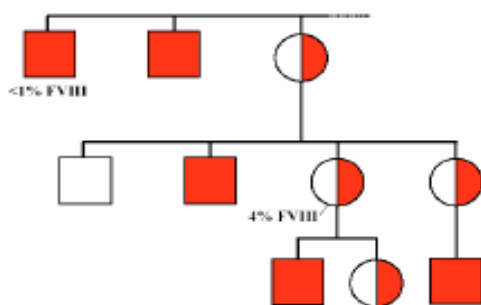


Figure 8

A female hemophiliac caused by a mosaic X chromosome deletion, a hemophiliac with 4% Factor IX, normal *caryotype*, 46XX on white blood cell, there were no stigmata of Turner's syndrome, the mucous and fibroblast biopsy founded a mosaic *caryotype* of 46XX, 45XO, and most of tissue chromosome 45XO produce the Factor IX.<sup>7</sup>

Cutler (2004) reported a case investigation regarding male with severe sporadic hemophilia-B, showed that his mother had a deletion mutation at her white blood cells. The mosaic mutation on white blood cells also happened to his grandfather and her aunty from his mother's side. This case

report implied that his grandfather was an individual with mosaic both in somatic cells and also germ-line cells.<sup>26</sup>

Other possibilities are this patient may have acquired inhibitors in hemophilia-B or VWD. Inhibitors in hemophilia develops in 25% hemophiliac patients after several substitution therapy, but much lower in hemophilia-B where the incidence is 3-5% in severe hemophilia-B and even lower in mild-moderate hemophilia patients. An inhibitors is diagnose when they not responding to infusion therapy and should be confirmed in laboratory with Bethesda assay for factor IX. Inhibitor is present when prolonged coagulation test is not corrected after mixing with normal plasma. Although mixing test is not done due to lack of services, probability our patient has the inhibitor is least likely because she has never been transfused with factor IX prior to this admission.<sup>27-28</sup>

VWD also known as pseudo-hemophilia is the most frequent congenital bleeding disorders worldwide, affecting almost 1% of population.<sup>29</sup> Its clinical presentation similar to hemophilia especially 2N VWD type because qualitative defect of VWF (Von Willebrand Factor) compromise factor VIII binding site lead to bleeding episodes involving joint and deep tissue representing classical hemophilia. VWF abnormality also affects platelet plugs formation during primary hemostasis response. As a consequent, their bleeding type mimicking to those seen in platelet disorders such as easy bruising, skin bleeding. Although examination of VWF is not performed, VWD is unlikely in our case. Normal bleeding time test and normal level of her thrombocytes were not suitable for VWD.

Besides counseling, education, and supportive therapy, substitution therapy is the specific therapy based on the pathophysiology of the diseases since genetic therapy is not available. The substitution therapy that can be given are: (i) a Fresh Frozen Plasma (FFP) which contains all of blood coagulating factors, could be administered whilst the diagnose still undefined and if the concentrate of factor IX is still unavailable. Every 1 ml of fresh frozen plasma contains 1 unit of factor IX (15-20 ml/kg of body weight), (ii) Prothrombin Complex Concentrates (PCCs) that contains factors II, VII, IX and X (70-80 IU/kg of body weight), (iii) Factor IX concentrate could be administered in the form of plasma derivate or recombinant, each unit/ body weight would increase the activity of factor IX 1 IU/dL average for plasma-derivate type and 0,8 IU/dL for the recombinant type. Recombinant factor IX was made by a specific cell that have been processed with the recombinant DNA technology, and each vial contains 250-2000 unit. The substitution therapy will be stopped when there is no bleeding manifestation.<sup>1,8</sup> Gene transfer is a

future therapy for hemophilic, which is still a developing biological molecular therapy, but until now it can not changes hemophilic phenotype.<sup>30</sup> For our patient, the counseling, education, supportive therapy for acute bleeding management and fresh frozen plasma has been administered.

## RESUME

Women 38 year old suspected of having sporadic hemophilia based on repeatedly bleeding episodes due to low level of factor IX activity (1.8%) supported by no history of hemophila running in the family neither ascendant nor descendent. Definite diagnosis through DNA mutation analysis and other genetics testing was not carried out. The assumptions of the etiology of female hemophilic were (i) new mutation of germ cell on both parent, (ii) new mutation of germ cell on one of parent (ovum or sperm) with non random or extreme inactivation (lyonization) of normal X chromosome, (iii) mutation of female hemophilic zygote (at the early stage of embryogenesis) with non random or extreme inactivation of normal X chromosome, (iv) mosaic deletion of X chromosome, karyotype 46XX, 45XO and most of tissue that produce IX factor (45XO). VWD and acquired hemophilia have also been considered but less likely to be the case. Despite abnormal coagulation tests, no other significant laboratory and physical findings were found. Counseling, education, supportive therapy for acute bleeding management and fresh frozen plasma has been given to this patient and she finally passed away one year later because of cerebral bleeding.

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