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Review

J Hematol. 2024;13(4):137-141

Hemophilia and Other Congenital Coagulopathies in Women

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Abstract

Deficiencies of factor VIII (FVIII)/von Willebrand factor (VWF) or factor IX (FIX) are underappreciated as potential reasons for heavy menstrual bleeding, recurrent nosebleeds, and easy bruising in girls and women. Bleeding is usually not attributed to hemophilia because clinically significant deficiencies in clotting factors VIII and IX are thought to only affect males. While severe hemophilia is more commonly observed in boys and men, women with mutations in the FVIII or FIX genes (*f8* or *f9)* may have widespread bruising and even joint bleeding. They might be heterozygotes with a hemophilic allele on one X chromosome and a normal allele on the other or rarely homozygotes with hemophilic alleles on both X chromosomes. If most or all of an X chromosome is missing (X-chromosome hemizygosity or Turner syndrome) and a hemophilic mutation is present on the other X chromosome, the affected woman will have a severe bleeding tendency. Other inherited disorders that affect women as well as men are von Willebrand disease, combined deficiencies of factor V (FV) and FVIII, and combined deficiencies of the vitamin K-dependent clotting factors. Women as well as men with autoimmune diseases or even those previously well might acquire a severe hemorrhagic disorder due to autoantibodies directed against FVIII, FIX, or VWF. Lastly, easy bruising and mildly decreased FVIII levels are occasionally observed in both men and women with hypothyroidism or panhypopituitarism. The purpose of this brief review is to increase clinician awareness that these bleeding disorders can affect girls and women. An accurate diagnosis and appropriate therapy will greatly benefit patients and their families.

Keywords: Female hemophilia; Hemophilia heterozygotes; X-chromosome hemizygosity; Autoimmune hemophilia

Introduction

Hemophilia, an inherited bleeding disorder, is due to a deficiency or defect in clotting factors VIII (FVIII) or IX (FIX). FVIII hemophilia (hemophilia A, classical hemophilia) occurs in 1 in 5,000 male births and FIX hemophilia (hemophilia B, Christmas disease) in 1 in 30,000 [1]. The genes governing the synthesis of these proteins reside on the X chromosome; when they are mutated, the bleeding phenotype is infrequently expressed in females because they have an unmutated allele on their other X chromosome, i.e., they are heterozygous. However, there are reports of female infants and young girls who bruise easily, have nose, gum, and joint bleeding, and laboratory evaluation discloses FVIII or FIX levels clearly below the normal range (50% to 150%). A factor level < 40% was reported in 1,976 females attending US Hemophilia Treatment Centers between 2012 and 2022 [2]. They represented 6.5% of the individuals seen at the centers; most (69%) were deficient in FVIII. Severe and moderately severe hemophilia, defined by factor levels ≤ 0.05 IU/mL, were noted in 8% of those with FVIII deficiency and 4.6% of those with FIX deficiency. Potential diagnoses in these girls and women are listed in Table 1, and a definitive review of the genetic causes of hemophilia in females was published by Miller et al in 2021 [3].

Hemophilia Heterozygotes (Carriers)

Heterozygous females have a hemophilic allele on one X chromosome and a normal allele on the other X chromosome. Their fathers have hemophilia, or their mothers have hemophilic sons or other close relatives affected by this disorder. In the absence of a family history, targeted high-throughput gene sequencing will usually reveal *f8* or *f9* mutations [4]. A recent review estimated that there are as many as 96,000 women who are heterozygous for hemophilia A (FVIII deficiency) in the USA [5].

How likely is a bleeding tendency in these heterozygotes? Random inactivation of one of the X chromosomes in each cell (the Lyon hypothesis [6]) predicts that heterozygotes should have half the normal amount of FVIII or FIX, i.e., 0.5 IU/mL. However, the distribution of clotting factor levels in heterozygotes is described by a bell-shaped curve; in one survey of 1,528 heterozygotes for hemophilia A, 532(35%) had FVIII levels < 0.4 IU/mL [7]. In these individuals, skewing of X chromosome inactivation (extreme lyonization) results in clotting factor concentrations low enough to be associated with a bleeding phenotype [8]. Miller et al [3] describe several other circumstances that could account for the inactivation of the X chromosome bearing the normal allele and expression of only the hemophilic allele. A survey performed by Lusher et al [9] reported 10 FVIII heterozygotes with FVIII levels of 0.01 - 0.09 IU/mL, and six FIX heterozygotes with values of 0.02 - 0.1 IU/mL. All 16 had excessive bruising and several

Manuscript submitted June 8, 2024, accepted July 10, 2024
Published online August 31, 2024

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doi: https://doi.org/10.14740/jh1298

Table 1. Disorders Associated With FVIII or FIX Deficiency Affecting Girls and Women

Heterozygosity or hemizygosity for one or more hemophilic alleles
Homozygosity or compound heterozygosity
X-chromosome hemizgosity
Acquired hemophilia due to a FVIII or FIX autoantibody[a]
von Willebrand disease[a]
Acquired von Willebrand syndrome[a]
Combined FV/FVIII deficiency[a], combined deficiency of all vitamin K-dependent factors[a]
Hypothyroidism[a] and panhypopituitarism[a]

[a]These disorders also affect boys and men. FVIII: factor VIII; FIX: factor IX.

had hemarthroses. While epistaxis, easy bruising, and excessive bleeding with trauma regularly occur in hemophilic males with levels of 0.02 to 0.05 IU/mL, most of those having more than 0.05 IU/mL are asymptomatic. On the other hand, female heterozygotes with levels that are higher than 0.1 IU/mL often have heavy menstrual bleeding, postpartum hemorrhages, and other bleeding phenomena including hemarthroses [10-12]. Thus, in these girls and women, the level of clotting factor is not always an accurate predictor of bleeding [5].

Homozygosity and Compound Heterozygosity

If a father has hemophilia and the mother is a heterozygote, and the mother's hemophilic allele is passed on to their daughter, she will be homozygous if the parent's hemophilic mutations are concordant and a compound heterozygote if they are discordant. Miller et al [3] observed that compound heterozygosity can also occur when a hemophilia allele was inherited from one parent and a *de novo* mutated X chromosome was received from the other parent and provided several examples from the literature.

Homozygosity in a girl with severe hemophilia was reported as early as 1951 [13]. In another family, marriage between first cousins gave rise to daughters with hemorrhagic symptoms and FVIII levels less than 1% of normal; laboratory studies excluded von Willebrand disease (VWD) [14]. However, it is difficult to exclude carriership with severely skewed X-chromosome inactivation or X-chromosome deletions in these and other examples of female hemophilia reported in the older literature [15, 16]. Detailed genetic analyses are required to achieve an accurate diagnosis and identify asymptomatic family members who might be heterozygous for hemophilic mutations. In some cases, formal investigation of paternity might reveal a father affected by hemophilia.

X-Chromosome Hemizygosity

Hemizygosity describes individuals lacking all or most of an X chromosome. Turner syndrome is characterized by short stature, sexual immaturity, neck webbing, and a genetic profile of 45,X or 45,X/46,XX. Because the intact X chromosome comes from the mother in two-thirds of these individuals, a woman heterozygous for a hemophilic allele is likely to pass it on to her infant with Turner syndrome. Therefore, a bleeding phenotype might be anticipated in a female infant with Turner syndrome and a family history of hemophilia. Blag et al [17] describe the clinical and genetic features of 10 females with concomitant Turner syndrome and hemophilia. All had hemizygosity for the X chromosome or mosaic karyotypes; six had a serious bleeding disorder and the mutations detected in three of the six were intron 22 inversions characteristic of severe hemophilia.

Very low levels of FVIII and recurrent hemarthroses were reported in a girl with an aneuploid number of chromosomes (45/46) whose mother was a known hemophilia heterozygote; whether the X chromosome with the hemophilic allele was the only viable X chromosome in that patient was not established [18]. Nisen et al [19] described a female infant with ecchymoses, epistasis, and hemarthrosis. Her mother's identical twin sister had a son with severe FIX deficiency hemophilia. Studies revealed that the propositus had non-random inactivation of a structurally abnormal X chromosome, resulting in the expression of a hemophilic FIX gene on the other, structurally normal X chromosome.

Severe hemophilia was reported in a young woman whose father was similarly affected [20]. She inherited a microdeletion (2.3 Mb at Xp22.2) in one of her X chromosomes from an otherwise normal mother, resulting in the extreme skewing of X-inactivation possibly due to a survival disadvantage or cell-lethal mechanism. The girl had a bleeding disorder because the only X chromosome expressed in her cells was derived from her hemophilic father.

Acquired Hemophilia due to FVIII or FIX Autoantibodies

Rarely, pathogenic autoantibodies develop in women (and men) without a previous history of a bleeding disorder. FVIII autoantibodies have occurred in association with other autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus and have arisen during pregnancy and the postpartum period. New onset bruising and bleeding in a girl or woman, along with a markedly reduced level of FVIII or FIX, should raise suspicion of this diagnosis. Lulla et al [21] described a woman with severe postpartum hemorrhage as-

sociated with a FVIII autoantibody; transplacental transfer of this antibody to the newborn caused excessive bleeding after a minor surgical procedure.

VWD

A decreased level of FVIII in females is more commonly due to VWD than hemophilia. Normally, the von Willebrand factor (VWF) forms a complex with FVIII, prolonging its clearance from the circulation. When the VWF is deficient or defective, the formation of this FVIII/VWF complex is impaired and the half-life of FVIII is shortened, resulting in variably reduced levels of the clotting factor. In the most severe form of VWD, type 3, individuals have no detectable VWF, and FVIII levels are less than 0.1 IU/mL. Another variant, type 2N (Normandy), has mutations affecting the FVIII binding site within the VWF N-terminal D'D3 domain; the FVIII deficiency that results is in the mild to moderate range. Patients with VWD bruise easily and their frequent epistaxis and heavy menstrual bleeding contribute to the development of iron-deficiency anemia. While bleeding in most patients is controlled by desmopressin infusions, VWF concentrates are required for those with type 2N or type 3 disease.

Acquired VWD

Individuals with systemic lupus erythematosus, monoclonal gammopathies, and lymphoproliferative syndromes can develop autoantibodies to VWF [22]. The clearance of antibodies bound to VWF/FVIII reduces the levels of both VWF and FVIII and can be differentiated from a synthetic defect in VWF by noting an increase in the ratio of VWF propeptide to VWF antigen [23]. Patients with autoantibodies to VWF have mucosal bleeding, and there is often excessive blood loss complicating surgery or trauma. Modalities for controlling bleeding include desmopressin, FVIII/VWF concentrates, and intravenous immunoglobulin. A few other causes of acquired von Willebrand syndrome (aVWS) are hypothyroidism (see below), Wilms tumor, aortic stenosis, and myeloproliferative disorders.

Combined FV and FVIII Deficiency/Combined Vitamin K-Dependent Factor Deficiency

Mutations in either *LMAN1* and *MCFD2* are the cause of a combined deficiency of FV and FVIII. MCFD2 binds these clotting factors and LMAN1 is the chaperone of MCFD2; the complex of both proteins transports FV and FVIII from the endoplasmic reticulum to the Golgi apparatus of the cell [24]. The activated partial thromboplastin time (aPTT) and prothrombin time (PT) are prolonged and the FV and FVIII levels range from 5% to 30%; bleeding with minor trauma, menorrhagia, and postpartum hemorrhage are reported in affected women [25]. Therapy includes desmopressin or recombinant FVIII concentrates to raise FVIII levels, and fresh frozen plasma to supplement FV [26].

Decreased levels of FIX are encountered in individuals with combined deficiencies of the vitamin K-dependent clotting factors [27]. Mutations in the genes for the vitamin K carboxylase or reductase prevent carboxylation of clotting factors II, VII, IX, and X, rendering them inactive and resulting in a bleeding phenotype. The differential diagnosis includes vitamin K deficiency, liver disease, and surreptitious ingestion of warfarin/rat poison. Treatment with vitamin K_1 enables completion of clotting factor synthesis and ameliorates bleeding.

Hypothyroidism

Hypothyroid women and girls bruise easily and have menorrhagia. They have reduced levels of VWF and mildly decreased FVIII concentrations [28]. A systematic review in 2008 noted that the median value for VWF in 24 patients was only 28 U/dL, and FVIII ranged from 9 to 74 U/dL in 16 patients. These results are consistent with the diagnosis of aVWS [29]. A prospective study of 90 consecutive patients with overt hypothyroidism before or within 48 h of replacement therapy revealed that 33% met the criteria for aVWS [30]. The bleeding scores in these patients were negatively correlated with the levels of VWF. In addition, hypothyroid patients have evidence of excessive fibrinolytic activity [31]. Desmopressin administration is effective in controlling acute bleeding, and thyroid replacement is the definitive management [32].

Panhypopituitarism with central hypothyroidism is also associated with decreased levels of FVIII and VWF and has been described in a 9-year-old boy with multiple congenital anomalies and in a 40-year-old woman with Sheehan's syndrome [33, 34].

Conclusions

A report of a decreased concentration of either FVIII or FIX in a female should raise the consideration of the possibility of hemophilia, especially if there is a history of easy bruising, excessive bleeding after dental or other surgery, and hemarthroses. A family history of bleeding episodes in one or more male relatives and marriages between cousins would be contributory. The differential diagnosis includes VWD in those with a decreased FVIII, as well as some of the other disorders described previously. Genetic studies should be obtained, not only of the patient but also of both parents, to identify the hemophilia-causing mutation and in whom it might have originated [3, 35]. Once a specific diagnosis is established, appropriate management for bleeding can be provided and genetic counselling initiated. Lastly, levels of FVIII and VWF might be decreased in acquired disorders such as autoimmune diseases, hypothyroidism, and panhypopituitarism, and unusual bleeding in these conditions should be fully investigated.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Data Availability

The author declares that data supporting the findings of this study are available within the article.

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