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Menorrhagia in inherited bleeding disorders in Iraqi women

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Abstract:

BACKGROUND: Menorrhagia, or excessive menstrual bleeding, is a common symptom in women with inherited bleeding disorders; they are conditions where the blood ability to clot is impaired. Some of the common bleeding disorders include von Willebrand disease (VWD), clotting factor deficiencies, and platelet function disorders.

OBJECTIVE: To assess different types of inherited bleeding disorders in women with menorrhagia referred to the National Center of Hematology/Mustansiriyah University in Baghdad/Iraq.

PATIENTS AND METHODS: A prospective study was carried out on 193 women who had experienced menorrhagia for a duration of 3 years, from 2020 to 2023. These women sought consultation at the National Centre of Hematology/Mustansiriyah University. All participants were diagnosed through various laboratory tests, including complete blood count, blood film, blood group and Rh, bleeding time, prothrombin time, activated partial thromboplastin time, fibrinogen level, factor assay, von Willebrand factor antigen using ELISA technique, ristocetin cofactor, and platelet function test.

RESULTS: Out of the 193 women with menorrhagia who participated in this study, the majority of whom had an unidentified cause (36.3%), followed by VWD (30.1%) and platelet function disorders (21.2%). Other bleeding disorders (thrombocytopenia and factors deficiencies) were 5.7% and 6.7%, respectively. Furthermore, the results showed that there was a significant difference in family history and consanguinity between patients with a hereditary bleeding disorder and nonhereditary bleeding disorder ($P < 0.001$).

CONCLUSIONS: Fifty eight percent of females with Menorrhagia in this study have inherited bleeding disorders(IBDs), VWD, and thrombasthenia account for 51.3% are the most common causes of inherit bleeding disorder (IBD). Consanguineous marriage should be discouraged in Iraqi society to reduce such inherited diseases.

Keywords:

Bleeding disorders, Iraq, menorrhagia, platelet dysfunction, von Willebrand disease

Introduction

Clinically, menorrhagia is defined as a period of abnormally heavy menstrual bleeding that lasts longer than 7 days and exceeds 80 ml/cycle.[1] The gynecological condition known as menorrhagia is rather frequent. Among women, Inherited bleeding disorders (IBDs) have a significant prevalence.[2] Menorrhagia can arise from a diverse range of causes, and a gynecological evaluation is essential to customize treatment for each patient and avoid intrusive procedures that may be ineffective. Problems with the hypothalamic–pituitary–ovarian (HPO) axis, which leads to anovulation and menorrhagia, are prevalent in adolescents. Menorrhagia affects over 75% of young women, and according to some scientists, the HPO axis is undeveloped as a result. One typical reason for heavy menstrual bleeding in adolescents is the underdevelopment of the HPO axis, leading to lack of ovulation. Some specialists suggest that over 75% of occurrences of menorrhagia in young individuals are caused by immaturity of

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the HPO axis.[3] Additional factors that might cause excessive menstrual bleeding during adolescence include polycystic ovarian disease, hypothyroidism, and tuberculosis of the vaginal tract.[4] Furthermore, menorrhagia has been associated with inherited bleeding diseases to a substantial extent.[5]

Possible contributing factors to heavy menstrual bleeding in adolescents include polycystic ovarian disease, hypothyroidism, and tuberculosis affecting the vaginal system.[6] von Willebrand disease (VWD) affects between 5% and 24% of women with menorrhagia.[7] Platelet function deficiencies are the second most prevalent inherited bleeding disorders (IBDs) among women and girls experiencing excessive menstrual bleeding, with a prevalence ranging from 4% to 44%. Mild hemophilia A or B, traditionally referred to as symptomatic carriers, together with uncommon coagulation factor deficits, are infrequent types of inherited bleeding disorders (IBDs). Menorrhagia is common in women with bleeding disorders. Menorrhagia impacts a significant percentage of women with various bleeding disorders, including VWD, platelet failure, symptomatic hemophilia, and uncommon factor deficits.[1] Under the effect of progesterone, platelets' activities were changed during the ovarian cycle on the von Willebrand factor (vWF) and estrogen.[8] The delicate balance between coagulation and fibrinolytic cascades.[9] Women with menorrhagia tend to be more likely than the overall population to have abnormalities of platelet function, such as VWD.[6] The aim of this study as to assess different types of inherited bleeding disorders in women with menorrhagia referred to the National Center of Hematology/Mustansiriyah University in Baghdad.

Patients and Methods

This cross-sectional study was conducted on 193 girls and women with menorrhagia suspected to have IBDs for <3 years' duration; patients were referred consulting the National Center of Hematology/Mustansiriyah University between September 2020 and June 2023. All patients were provided with written informed consent for study participation.

Inclusion criteria

All female suspected with IBDs have menorrhagia (if she had other mucocutaneous bleeding and with positive family history of bleeding), with normal renal function and liver function tests.

Exclusion criteria

All female with abnormal hormonal disturbances, gynecological causes of menorrhagia (use of intrauterine devices and use of certain medications, including anticoagulants, non-steroidal anti-inflammatory agents) were excluded.

Each patient underwent a comprehensive assessment of their bleeding history, and menorrhagia was confirmed by utilizing scores on pictorial blood assessment charts (PBAC) (PBAC score >100) regarded as menorrhagia with a blood loss of >80 ml/cycle. Face-to-face interview with patients:

- If lightly stained pads or tampons obtained a score of 1
- If moderately stained pads a score of 5
- If soaked pads score of 20.

The information regarding family history, consanguinity, and residency were documented, and all patients had been examined by the same physician.

Laboratory investigation

The whole blood count was assessed using a hematology autoanalyzer, which included an examination of the blood film and determination of the blood group and Rh factor. The collection of venous blood for coagulation testing involved using Vacutainer tubes containing a solution of 0.105 M sodium citrate. The plasma was then separated from the blood. Coagulation assays, including prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, and factors assay (Factor: I, II, V, VII, VIII, IX, X, XI ,were done according to PT and /or APPT results), by using a coagulometer (Stat max, Stago, France) within 3 hours of blood collection.

The plasma samples were stored at temperature of -80°C until they were analyzed for VWF: Ag level using the sandwich ELISA method (Stago, France). The platelet function test (Bio/Data, USA), was conducted using ADP (2.0x10-5M), Collagen (0.19mg/ml), and Ristocetin at both low dose (0.5 mg) and high dose (1.2 mg) by using platelet Aggregation profiler PAP -8E (Bio/Data, USA). The ristocetin cofactor assay (Bio/Data, USA) was performed using light transmission aggregometry with the PAP-8E Platelet Aggregation Profiler (Bio/Data, USA).

This study was reviewed and approved by ethical committee of scientific council of National Hematology Center. All patients were signed written informed consent before enrollment in the study.

Statistical analysis

The statistical analysis was conducted using the software package SPSS IBM Corp., Released 2021. IBM SPSS Statistics for Windows, Version 28.0. (IBM Corp., Armonk, NY). Demographic data were characterized using descriptive statistics P-value <0.05.

Results

One hundred ninety-three patients (women and girls) ranged from 11 to 53 years with mean age (23.2±10.93),

36.8% of patients were < 18 years and 63.2% of patients were ≥ 18 years are presented. The demographic characteristics are shown in Table 1.

There were statistically significant results regarding positive family history among women diagnosed with inherited bleeding disorders which represented (48.97 %) of total women and women with non-inherited disorders (9.9%), with *P*-value <0.001 as shown in Table 2, Figure 1.

Regarding consanguinity, there were statistically significant differences between women with inherited bleeding disorders consanguinity (51.82 %) of total women and non-inherited bleeding disorders which represent (10.36%), *P*-value < 0.001, as shown in Table 3, Figure 2.

The most common cause of menorrhagia in women with bleeding disorders in the current study was VWD in 58 (30.1%), followed by Platelet function disorders in 41 (21.2%), and factors deficiency, were in 13 (6.7%), thrombocytopenia were found in 11 (5.7%) of patients While in 70 (36.3%) of patients with menorrhagia was undefined cause, as illustrated in Table 4.

Discussion

Menorrhagia is a common clinical problem and affects the quality of life in women with IBDs. Inherited bleeding disorders are conditions where the blood's ability to clot is impaired. Some of the common bleeding disorders include VWD, hemophilia, and platelet function disorders.[10] Patients with inherited bleeding disorders can present at puberty, with menorrhagia requiring immediate medical attention.[11] A British study conducted by Kadir RA *et al*.[12] found that 17% of women with menorrhagia had an inherited bleeding condition, with VWD being the most prevalent. Menorrhagia impacted 193 women admitted to our facility who were thought to have IBDs. In current study 36.8% of these patients were under 18 years old while 63.2% was more than 18 years old, this result differ from findings of Kiliç *et al* (2023) in Turkey,[13] who stated that 65% of the patients were younger than 18 years. The majority of our patients had an unidentified cause (36.3%), this result is in accordance with James (2007) who concluded that a specific reason is found in less than 50% of patients suffering from menorrhagia.[14] The most common cause of IBDs in women with menorrhagia in this study is VWD (30.1%), this result is agree with other studies which showed menorrhagia was 5%-36% VWD patients.[15,16]

Menorrhagia is presenting symptom in 51% of patients with Bernard Soulier syndrome (BSS) and 13% - 98% of people with Glanzmann's thrombasthenia (GT).[13] Typically, these patients arrive with significant epistaxis and gum bleeding.[13] In the current study, platelet function disorders which include GT, BSS, and storage pool disease were identified in 21.2% of women with

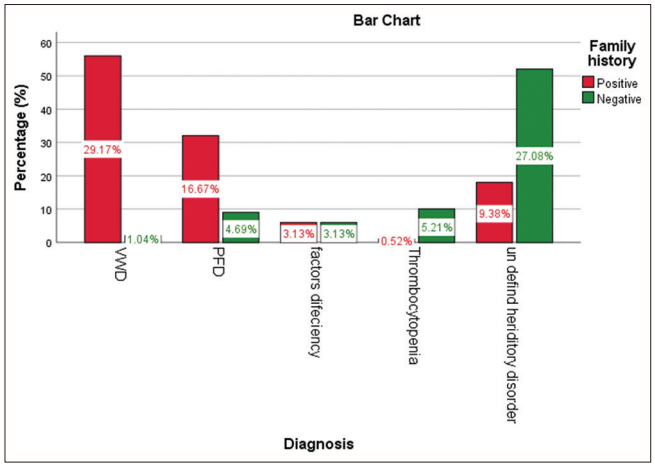

Figure 1: The percentage of family history among women with different diagnoses. VWD: Von Willebrand disease, PFD: Platelet function disorders

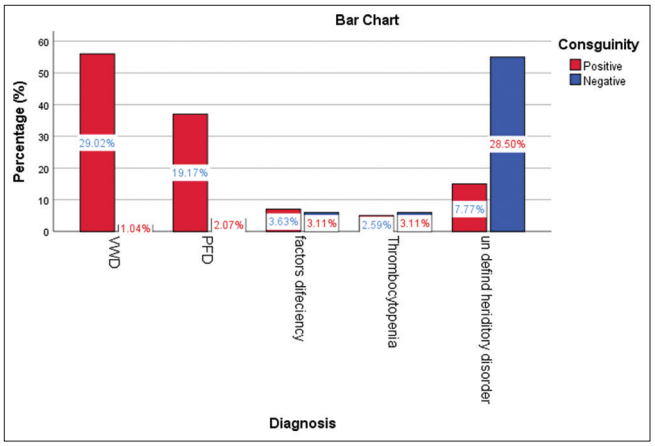

Figure 2: The percentages of consanguinity among women with different diagnoses. VWD: Von Willebrand disease, PFD: Platelet function disorders

Table 1: Demographic characteristics in women with menorrhagia

Bleeding disorders	*n*=193	Age (mean±SD)	Family history (%)	Consanguinity (%)
VWD	58	25.7±10.9	29.17	29.02
Platelet function disorder	41	21.1±9.0	16.67	19.17
Thrombocytopenia	11	25.1±10.1	0.52	2.59
Factors deficiency	13	21.9±9.7	3.13	3.63
Undefined cause	70	24.3±9.9	9.38	7.77
Total	193		58.87	62.18

VWD=Von Willebrand disease, SD=Standard deviation

Table 2: The differences between women with Inherited bleeding disorder and Non-inherited bleeding disorder to family history

Groups	Total number	Family history percentage	χ^2	*P*
Inherited bleeding disorders	112	48.97	97.98	<0.001
Non-inherited bleeding disorders	81	9.9		

Table 3: The differences between women with Inherited bleeding disorder and Non-inherited bleeding disorder to consanguinity

	Number	Consanguinity percentage	χ^2	*P*
Inherited bleeding disorder	112	51.82	93.9	<0.001
Non-inherited bleeding disorder	81	10.36		

Table 4: Prevalence of inherited bleeding disorders in women with menorrhagia

Bleeding disorder	Menorrhagia, *n* (%)
VWD	58 (30.1)
Platelet function disorder	41 (21.2)
Factors deficiency	13 (6.7)
Thrombocytopenia	11 (5.7)
Undefined cause	70 (36.3)
Total number	193 (100)

VWD: Von Willebrand disease

menorrhagia who also had epistaxis and gum bleeding. Thrombocytopenia and other factors deficiencies such as(hemophilia (A and B), fibrinogen, factor VII, and Factor XIII deficiency) were (6.7%), A research by Kiliç SÇ in Turkey found that 20% of patients with menorrhagia had bleeding problems, including 1 instance of type 3 VWD, 2 cases of low VWF: Ag, 1 case of suspected VWD, 3 of BSS, 2 of GT, 2 of ITP, and 1 of congenital factor VII deficiency.(13) . In a previous study in Iraq by Al-Rahal NK.(2018Year) Found that out of 256 patients with IBDs, 94 had Platelet function disorders with only 2 cases with factor XI deficiency.[17] In UK The frequency of VWD and FXI deficiency were 13% and 4% respectively, because of a high proportion of Jewish women with a high prevalence of factor XI deficiency were referred.[18] Under the effect of progesterone, platelets' activities were changed during the ovarian cycle on the vWF and estrogen.[8] The delicate balance between the coagulation and fibrinolytic cascades is what leads to hemostasis.[9,19] In Saudi Arabia a cross sectional study was conducted on adolescent girls, 30.8% of them diagnosed with IBDs (five cases of probable VWD or low level of vWF:Ag and/or vWF:RCo, two cases of probable platelet dysfunction, and one case of factor V deficiency).[19] Susan H. from Germany found that among women with bleeding disorders, the prevalence of menorrhagia varies from 32% -100% in cases of VWD, 5% - 98% in cases of platelet dysfunction, and 35% - 70% in cases of rare factor insufficiency.[20] R Saxena *et al*[21] In India studied 337 women with menorrhagia suspected to have an inherited bleeding disorder; He concluded that although hereditary platelet function defects constitute a large majority of women with menorrhagia in (83.9%) but vWD and other factors deficiency were found in (11.9%), (1.5%) respectively. In our study, thrombocytopenia was found in 5.7% of patients. In the autoimmune condition known as ITP, platelets and megakaryocytes are attacked by autoantibodies. This causes thrombocytopenia and occasionally abnormalities in platelet function. Petechiae, bruising, epistaxis, and gum bleeding are some of the most typical clinical signs. Since ITP usually affects women of reproductive age, menorrhagia is a less commonly noted symptom that may be quite important.[22,23] The family history and consanguinity among patients are highly related to the diagnosis of women with menorrhagia, which makes it one of the most effective risk factors that is life-threatening implications, and since consanguinity is high in patients with inherited bleeding disorders in Iraq, this can explain emergence of life-threatening autosomal recessive inherited diseases in our patients in Iraq.[17]

Conclusions

- Fifty-eight of females with menorrhagia in this study have IBDs, most of them (51.3%) was VWD, and thrombasthenia
- Consanguineous marriage should be discouraged in Iraqi society to reduce such inherited diseases
- There is a need to expand awareness about IBDs to hasten early diagnosis and mitigate the occurrence of bleeding and their complications
- Although there is improvement in management and diagnosis of IBDs in Iraq, there is more to be done.

Recommendations

We recommend that screening tests for hemostasis should be performed to all females in a specialized center who, have other bleeding history, with positive family history. In addition to education, genetic counseling should be considered to lessen the prevalence of such bleeding disorders.

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Conflicts of interest

There are no conflicts of interest.

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