Journal of Rawalpindi Medical College (JRMC); 2010;14(1):2-6

Clinico- haematological spectrum of females with inherited Bleeding Disorders

Nadeem Ikram* , Tahira Zafar**, Arshad Ali Sabir***, Khalid Hassan**** , Samina Amanat *****

* Department of Pathology, Rawalpindi Medical College
** Department of Pathology, Islamabad Medical and Dental College, Islamabad
*** Department of Community Medicine , Rawalpindi Medical College.
**** Department of Pathology , Pakistan Institute of Medical Sciences , Islamabad
***** Department of Pathology, Pakistan Atomic Energy Commission Hospital, Islamabad

Abstract

Background: Inherited bleeding disorders in females are under-diagnosed, eventually leading to multiple problems. This situation is further worsened by the inadequate information , non – availability of diagnostic facilities and low awareness on the clinical side

Methods: In this non – interventional descriptive study , females with inherited bleeding disorders were assessed. Clinical presentations, demographic data and management received was recorded. Complete blood counts, prothrombin time, activated partial thromboplastin time, thrombin time and platelet function studies were performed, where required..

Results: In all the patients with inherited bleeding disorders , females constituted 16.85%. von Willebrand disease was the commonest (50.84%) out of all inherited bleeding disorders in females. In rest of the females autosomal recessive coagulation defects and platelet function defects constituted 25.42% and 23.72%, respectively. Majority of the females (83.04%) were below 17 years of age. Menorrhagia (46.87%) was the commonest clinical episode. Spontaneous bleed was seen in 95% episodes. Majority of the episodes (94.14%) were soft tissue bleeding episodes and joint bleeds were minimal (5.68%). Tranexamic acid was the most commonly used therapeutic agent . Surgical intervention was employed in 18 episodes.

Conclusion: Females with inherited bleeding disorders have severely impaired quality of life , fail to get proper management and go through unwanted surgeries (D&C; Hysterectomies).

Introduction

Very little information is available regarding gynaecological and obstetric problems in females with inherited bleeding disorders [1] Estimates suggest that 10 to 20% of women with menorrhagia have an underlying inherited bleeding disorder[2,3]. Menorrhagia is the most common manifestation seen in women with inherited bleeding disorders, but it is not the only abnormality. Females in their child bearing years are more likely to manifest an inherited bleeding disorder than premenarcheal or postmenopausal females. During pregnancy there is greater risk of miscarriage and bleeding complications. At the time of child birth, women with bleeding disorders appear to be more likely to experience postpartum haemorrhage, particularly delayed or secondary postpartum haemorrhage. Vaginal or vulvar haematomas, extremely rare in women without bleeding disorder, are not uncommon. Women with bleeding disorders are more likely to undergo a hysterectomy and more likely to have this operation at a younger age. Most of the times hysterectomies in these patients are performed in ignorance, rather than an option. These women appear to be at an increased risk of developing haemorrhagic ovarian cysts and possibly endometriosis. As they grow older, they may be more likely to manifest conditions, which present with bleeding such as fibroids, endometrial hyperplasia and polyps. While women with bleeding disorders are at risk for the same obstetrical and gynaecological problems that affect all women, they appear to be disproportionately affected by conditions that manifest with bleeding.[4] With this background, an overview of common inherited bleeding disorders, in females, focusing on their clinical manifestations, complications, diagnosis, treatment options and hindrances in their management can be considered as a likely objective to explore.

Patients and Methods

In this non – interventional descriptive study, females with inherited bleeding disorders presenting to Haemophilia Patients Welfare Society, Rawalpindi/Islamabad chapter and District Head Quarters Hospital Rawalpindi were analyzed. Demographic data, presenting episodes, diagnostic

evaluation and treatment received were recorded .Diagnosis was established on the basis of Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) , Thrombin Time (TT), Bleeding Time (BT), Clotting Time (CT), factor level estimation ,platelet count , platelet aggregation studies and examination of peripheral smear. Mixing studies were performed by using aged serum (24 hours old serum kept at 37 ^{0} C) and adsorbed plasma (normal plasma adsorbed by barium sulphate). Factor levels were estimated by using commercially available deficient plasmas. Platelet aggregation studies were performed by collecting 10 ml of blood in sodium citrate. Platelet rich plasma (PRP) was prepared by centrifuging the samples at 250 xg and 1500 xg respectively for ten minutes. The aggregation pattern was studied against different agonists (ADP, Epinephrine, Ristocetin, Collagen)

Results

Von Willebrand disease was the commonest ,followed by Glanzmann's thrombasthenia (Table1). Age group from 6 to 15 years constituted the main patient's group (Table 2) Menorrhagia was the most frequent presentation (46.87%) . Majority of the episodes were soft tissue bleeds. Joint bleeds were seen in 6.8% episodes. One patient died because of post partum bleed.(Table 3). Three patients presented with an acute abdomen due to haemorrhagic ovarian cyst.

Table 1: Distribution of females with inherited bleeding disorders

Total number of patients with inherited bleeding disorders = 350
Female patients with inherited bleeding disorders = 59/350(16.85%)

Disease	Number of Patients(%)
von Willebrand Disease	30/59 (50.84%)
Glanzman's Thrombasthenia	9/59 (15.25%)
Factor V Deficiency	7/59 (11.86%)
Factor X Deficiency	4/59 (6.77%)
Factor XIII Deficiency	3/59 (5.08%)
Bernard Soulier Syndrome	5/59 (8.47%)
Factor XI Deficiency	1/59 (1.69%)

Table 2: Inherited bleeding disorders in females: Age distribution

Age	Number of patients (%)
Less than 5 years	10/59 (16.94%)
6 – 15 years	39/ 59 (66.10%)
16 – 25 years	5 / 59 (8.47%)
26 – 35 years	2 / 59 (3.38%)
36 – 45 years	2 / 59 (3.38%)
46 – 55 years	1 / 59 (1.69%)

Table 3: Inherited bleeding disorders in females: Bleeding episodes

Menorrhagia	165/352 (46.87%)
Epistaxis	61/352 (17.32%)
Gum bleed	42/352 (11.93%)
Dental bleed	35/352 (9.94%)
Bruising	21/352 (5.96%)
Joint bleed	20/352 (5.68%)
Umbilical cord bleed	4/352 (1.13%)
Haemorrhagic ovarian cysts	4/352 (1.13%)
CNS bleed	2/352 (0.56%)
Postpartum bleed	1/352(0.28%)

Table 4: Platelet agggregation studies

	von Willebrand Disease	**Glanzmann's Thrombasthenia**	**Bernard Soulier Syndrome**
Platelet count	Normal	Normal	Decreased
Platelet size	Normal	Normal	Large
Aggregation with ADP	Normal	Absent	Normal
Aggregation with Collagen	Normal	Absent	Normal
Aggregation with Ristocetin	Absent	Normal	Absent

Aggregation with Epinephrine	Normal	Absent	Normal

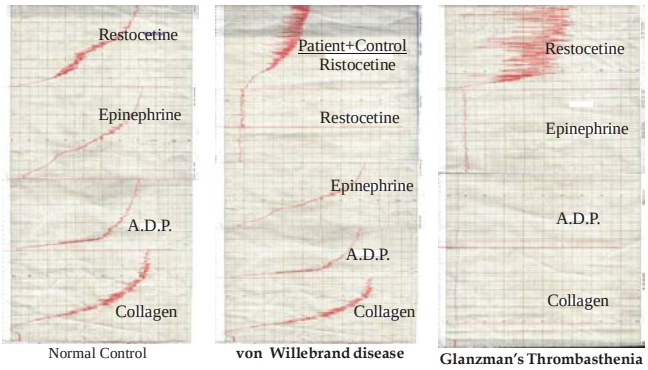

Fig1 : Platelet aggregation studies in females with inherited bleeding disorders

Table5: Inherited bleeding disorders in females: treatment received*

Treatment	Number of episodes
Tranexamic Acid	84 / 105
Fresh Frozen Plasma	40 / 105
Cryoprecipitate	10 / 105
Platelet's concentrates	32 / 105
Kaote	5 / 105
DDAVP	21 /105
Hormonal therapy	39 /105
Recombinant Factor VII	2 /105
Dilatation and Curettage	10 / 105
Laparotomies	5/105
Hysterectomies	3 /105

In laboratory evaluation prolonged bleeding time and APTT and normal PT , along with aggregation with all agonists, except Ristocetin , established the diagnosis of vWD. Bernard Soulier Syndrome and vWD gave similar results on platelet aggregation studies, but in vWD patient's plasma plus control plasma gave normal aggregation with Ristocetin and in Bernard Soulier Syndrome there was thrombocytopenia with giant platelets on peripheral smear (Table 4 ; fig 1). Tranexamic acid was the most commonly used therapeutic agent . Surgical intervention was employed in 18 episodes (Table 5)

Discussion

Despite their high prevalence, these disorders often remain undiagnosed, and particularly so unless significant iron deficiency anaemia, post operative bleeding and/ or transfusion occurs. Failure to recognize or even consider a diagnosis of a bleeding disorder either by patient or providers, limitation of available diagnostic tests ,which are complex to perform and interpret and the lack of available therapeutic agents to treat these disorders are a few of the mentionable obstacles [2].

The commonest inherited bleeding in females is von Willebrand Disease (vWD), followed by platelet function defects and some autosomal recessive coagulation factor deficiencies. Rarely female carriers of haemophilia can also have gynaecologic complications [1]. World wide vWD is considered as the most common inherited bleeding disorder [5] . Data on its epidemiology and impact in developing countries are limited. The biologic heterogeneity and variable presentation of vWD make diagnosis difficult. Although there is no accurate data of the prevalence of vWD in developing countries, available data suggests that the proportion of diagnosed cases is lower than the expected number, often accounting for only 6% to 13% of patients with hereditary bleeding disorders . The number is expected to be much higher in our set up due to high rate of consanguinity . The prevalence of different types of vWD is also not known which is essential for a proper management of these cases [6,7] . In an Indian study majority of the patients of vWD were type 3 (59.5%), with severe clinical manifestations . The high prevalence of type 3 and low prevalence of type 1 , which is in contrast to Western reports , can be ascribed to the consanguineous marriages , low awareness of the disease and also the under diagnosis of mild cases in this part of world [8] . The diagnosis of vWD is difficult because the intensity of symptoms is highly variable . At one end are type 3 patients who present in childhood with severe bleeding tendency and seek medical advice earlier and on the other end the patients with milder disease have very vague symptoms which they only tell when they are specifically asked . In between are the majority of patients who have unusual bleeding tendency but diagnosis is missed or delayed

In laboratory diagnosis of these problems time of testing in women's cycle is an important confounding factor. Fluctuating estrogen levels can

interfere in the estimation . Most of these women remain undiagnosed , diagnosed after a long delay or go through repeated laboratory evaluations before getting a proper diagnosis. It is recommended that blood testing, in these women, should be done during the first four days of menstrual period when their factor levels are lowest [9] .

With the exception of Haemophilia A and B , deficiencies of all the other plasma clotting proteins such as afibrinogenemia, hypofibrinogenemia, deficiencies of factor V and combined factor V and VIII , VII, X, XI, and XIII are inherited in an autosomal, mostly recessive, manner. Due to rarity of these deficiencies , which are expressed clinically only in homozygous or compound heterozygous , the type and severity of symptoms , the underlying molecular defects and the actual management of bleeding episodes are not well established as for haemophilia . In countries where consanguineous marriages are frequent recessive inherited coagulation deficiencies are more frequent. All these are associated with menorrhagia , recurrent abortions, haemorrhagic ovarian cysts , post partum haemorrhage and many other complications related with female reproductive system [10] .

As many as 10 to 20% of women with menorrhagia have an underlying bleeding disorder and in females with inherited bleeding disorders it is the commonest manifestation (table 3) [11]. Approximately 80% of women with inherited bleeding disorders suffer from menorrhagia . Menorrhagia in females with inherited bleeding disorders typically present at menarche , in contrast to other causes of menorrhagia [12] . In our data majority of patients were under 18 years of age (table 2) .It leads to under representation of menorrhagia in our data as compared to international data. Then in this part of the world majority of the cases of vWD are of type 3, with severe bleeding manifestations , while world wide type –1 is the commonest . It reflects under diagnosis of cases of vWD with mild menorrhagia . But it must be appreciated that over the time this percentage will increase, reflecting an upcoming disease load [5] .

In the present series the cases of haemorrhagic ovarian cysts underwent laparotomies. Surgeries in these cases might have been prevented if they had been diagnosed earlier and therapeutic/conservative management considered [13]. These cysts are due to excessive bleeding into the corpus luteum at the time of ovulation. Rupture of these cysts may result in haemoperitonium and secondary increased production of fibrin in the peritoneal cavity can be a major cause of increased formation of pelvic adhesions, external occlusion of the fallopian tubes, and destruction of the ovarian tissue. It can lead to reduced fertility in these patients [14,15] .

Post partum haemorrhage(PPH) is a catastrophic emergency in these females [16] .In present series one female with Glanzmann's thrombasthenia succumbed fatally to this complication . Women with risk factors for post partum haemorrhage can be identified in antenatal period. Pregnancy usually causes a rise in all of the plasma clotting factors except factor IX. So, often there is no bleeding problem during pregnancy . However following child birth, factor levels may fall rapidly and lead to post partum bleeding. Every labour suite should have appropriate PPH protocols, A multidisciplinary approach involving senior obstetrician, intensive care, haematologist and blood bank services are the corner stone in the management of PPH [17] .

Pregnancy in this group of women has been found to be associated with bleeding in early pregnancy , repeated miscarriages , abruption placenta , intrauterine demise and increased incidence of both primary and secondary postpartum haemorrhage .It is difficult to describe pregnancy and labour complications in individual manner [18] .

Many women with inherited bleeding disorders are on birth control pills or other hormonal therapies .This affects a women's ability to conceive. The long term impact of such prolonged hormonal therapy on conception is unknown. Some women with inherited bleeding disorders report excessive bleeding with intercourse , which may also cause difficulty in conception . The impact of inherited bleeding disorders on the implantation of fertilized embryo, into uterus, is not fully understood [1] .

Different treatment modalities are used in these females , depending upon the type of lesion and the nature of episode. Commonly employed agents are oral contraceptive pills(OCP), Tranexamic acid, desmopressin , and factor replacement. Desmopressin is contraindicated in vWD type 2b. and not useful in type 3. OCP are recommended as the first line treatment , especially in adolescent menorrhagia , and have been found to effective in majority of women [19] . Tranexamic acid is the most frequently used therapeutic agent in different bleeding episodes (Table 5) in a dose of 1 gm every six hour, for 3 – 4 days, during menstruation. It has been found effective in 54% of cases , when given over 2-3 menstrual cycles [18] . Commonly, non steroidal anti inflammatory medicines

are prescribed for control of menorrhagia , but their use in inherited bleeding disorders is usually contraindicated . Recently Recombinant factor VII (rF VII a) was launched, as a universal haemostatic agent, for varied haemorrhagic manifestations. The rFVIIa acts via tissue factor pathway. Limitations to its use are its short half life (2 hours) and high cost. It is contraindicated in disseminated intravascular coagulation [20] .

Conclusions

1. Bleeding manifestations severely affect quality of life of the women with inherited bleeding disorders, leading to a limitation in the performance of day to day chores, change in career, loss of faith on medical profession after being told for years their problems are not real, constant fatigue due to iron deficiency, painful menstruation or coitus, feeling of embarrassment, undue endometrial biopsies and hysterectomies. A proper management approach is usually rewarded with an overall change in the patient's personality.

2. Failure to investigate the women with inherited bleeding disorders limit the potential benefits of different therapies like, desmopressin (DDAVP), tranexamic acid, FFP and cryoprecipitate

3. The milder forms or carrier states of these disorders may remain asymptomatic. So, the diagnosis of inherited bleeding disorder in a female should provide clear prognostic and therapeutic indications that are distinct from the burdens associated with an unjustified genetic disease stigma, anxiety that may be caused by overestimates of a patient's bleeding risk and inappropriate resource expenditures. Therefore, at least for the mild from, it remains unclear whether the benefits of a diagnosis outweigh its disadvantages.

4. There is inadequate information, non-availability of diagnostic and management facilities and low level of awareness on the clinical side, about inherited bleeding disorders in females. Hence it is required to raise understanding about the intricacies of these disorders.

References

1. Paper R. Gynaecological complications in women with bleeding disorders. Treatment of Haemophilia, 2004; 6(5): 1 – 8
2. James AH, Ragni MW, Picozzi VJ. Bleeding disorders in premenopausal women :(another) public health crisis for haematology. Haematology 2006. American Society of Hematology Education Programme Book, 2006; 474 – 485
3. Demers C, Derz KC, David M . Gynaecological and obstetric management of women with inherited bleeding disorders .Int J Gynaecol Obstet, 2006; 95(1): 75 - 87
4. James AH. More than menorrhagia : a review of the obstetric and gynaecological manifestations of bleeding disorders . Haemophilia, 2005;1(4): 295 – 307.
5. Federci AB. Diagnosis of inherited von Willebrand disease: a clinical perspective. Semin Thromb Hemostasis,2006; 32(6): 555 - 565
6. Srivastava A. von Willebrand disease in the developing world. Semin Hematol, 2005; 42(1): 36 – 41
7. Trasi SA, Pathare AV, Shetty Sd, Ghosh K, Salvi V, Mohanty D . The spectrum of bleeding disorders in women with menorrhagia : a report from Western India . Ann Hematol, 2005: 84(5):339 – 342
8. Trasi S, Shetty S, Ghosh K, Mohanty D. Prevalence and spectrum of von Willebrand disease from Western India . Indian J Med Res, 2005;121(15): 628 - 630
9. Clement P. Women's experience with undiagnosed bleeding disorders. Parent empowerment news letter,2004;5:6-11
10. Vijapurkar L, Mota S, Shetty S , Ghosh K. Menorrhagia and reproductive health in rare bleeding disorders: a study from the Indian subcontinent . Haemophilia,2009; 15: 199 – 202
11. Edlund M , Bloomback M, von Schoultz B, Anderson D. On the value of menorrhagia as a predictor for coagulation disorders . Am J Haematol, 1996;5(1): 40 – 48
12. Ragni MV. Bleeding disorders in premenopausal women – the view of the hematologist . Hematology 2006- American society of hematology education programme book . 477 – 482
13. Radakovic B and Grgic O. von Willebrand disease and recurrent hemoperitoneum due to the rupture of haemorrhagic ovarian cysts. Hemophilia , 2009; 15: 607 – 609
14. Meschengieser SS, Alberto MF, Salvin J, Beronejo E, Lazzori MA. Recurrent haemoperitonium in mild von Willebrand disease . Blood Coagul Fibrinolysis, 207 – 209
15. Radakovic B & Grgic O. von Willebrand disease and recurrent hematoperitonium due to rupture of haemorrhagic ovarian cysts. Haemophilia, 2009; 15: 607 – 09
16. Kadir RA, Lee CA, Sabin CA, Pollard D, Economiodes DL. Pregnancy in women with von Willebrand disease or factor XI deficiency. Br J Obstet Gynarcol, 1998; 105(3):314 – 21
17. Hossain N. Postpartum haemorrhage . In Haematologic disorders in gynaecology and obstetrics. Sahmsi T, Hossain N,eds,2010. Najam printers, Karachi,Pakistan.p43.
18. Kulkarni AA, Lee CA, Kadir RA. Pregnancy in women with congenital factor VII defiicnecy. Haemophilia 2006; 12(4): 413 – 6
19. Lee CA, Chi C, Pavord SR, Maggs PH, Pollard D, Wood A, et al The obstetric and gynaecological management of women with inherited bleeding disorders review with guidelines produced by a taskforce of UK Haemophilia Centre Doctors Organization . Haemophilia, 2006;12(4): 301 – 36
20. Monoroe DM, Hoffman M, Allen GA, Roberts HR. The factor VII – platelet interplay:Effectiveness of recombinant factor VII-a in the treatment of bleeding in severe thrombocytopenia . Emin Thromb Hemost, 2000;26: 373 – 377.