Original Article

Prevalence of Rare and Common Bleeding Disorders in Kurdistan Province of Iran

Akbar Dorgalaleh[1], Jamal Rashid Panah[2], Bijan Varmaghani[3], Peyman Beigi[4], Abbas Ahmadi[5]*

Abstract

Background: Congenital bleeding disorders (CBD) are a group of coagulopathies with different clinical and laboratory features. The prevalence of these disorders in different parts of the world is variable. Iran as a country with a high rate of parental consanguinity has a high rate of CBDs. This study was to report the prevalence of these disorders in Kurdistan province, west of Iran.

Methods and materials: This descriptive study was conducted on patients suspected of a congenital bleeding disorder referred to hemophilia center of this province for evaluation of underlying bleeding diathesis. Diagnosis and classification of disorders were made by routine and specific laboratory tests.

Results: Out of 107 patients, 65.4% affected by common bleeding disorders (hemophilia A and B), 23.4% affected by rare bleeding disorders (RBDs) and 11.2% had inherited platelet disorders. Factor VII deficiency (64%) was the most common RBDs and 9 patients had von Willebrand disease. Out of three patients with inherited platelet disorders, two had Glanzmann thrombasthenia.

Conclusion: CBD pattern though has similar patterns with total pattern of the country, some of the inherited platelet disorders are more common in Kurdish province. Determination of prevalence and distribution of these disorders can improve health system planning and resource allocation.

Keywords: Congenital bleeding disorders, Rare bleeding disorders, Common bleeding disorders, inherited platelet disorders

1. Department of Hematology and Blood Transfusion, School of Allied Medicine, Iran University of Medical Sciences, Tehran, Iran
2. Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
3. Tehran Hear Center, Tehran University of Medical Sciences, Tehran, Iran
4. Department of Hematology and Blood Transfusion, Tarbiat Modares University, Tehran, Iran
5. Cellular and Molecular Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran

Corresponding Author: Abbas Ahmadi, Cellular and Molecular Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran
Email: abbasahmady1@gmail.com

Please cite this article as: Dorgalaleh A, Rashid Panah J, Varmaghani B, Beigi P, Ahmadi A. Prevalence of Rare and Common Bleeding Disorders in Kurdistan Province of Iran. J Cell Mol Anesth. 2019;4(4):107-11.

Introduction

Congenital bleeding disorders (CBDs) are a heterogeneous group of coagulopathies with various bleeding tendencies. Hemophilia A (HA), hemophilia B (HB) and von Willebrand's disease (vWD) are the most common which accounted for more than 90% of all CBDs (1). Other CBDs including factor (F) I, FII, FV, FVII, FX, FXI, FXIII, combined FV and FVIII, and combined vitamin K dependent factors deficiencies are rare bleeding disorders (RBDs) which account for 2% to 5% of all CBDs. The frequency of RBDs is varying between 1/500000 for FVII deficiency (FVIID) to 1/2000000 for FXIII (FXIIID) and FII deficiencies (FIID) (2). Inherited platelet function defects are another infrequent group of CBDs

that result from defects in platelet activation, adhesion, and aggregation (3). Although RBDs and inherited platelet disorders are rare, they are more frequent in an area such as Middle East countries with a high rate of consanguinity (2, 3). Iran has a high frequency of inherited bleeding disorder which can be related to an increased rate of parental consanguinity. Although some studies report the prevalence of CBDs in different regions of Iran, the precise distribution of these disorders is not established in all areas. Accurate data on the prevalence of these disorders in different regions of the country is necessary for health care programs. Therefore current study aimed to document the prevalence of CBDs in Kurdistan Province, west of Iran

Methods

Study subjects

This descriptive study was conducted on patients affected by CBDs who referred to hemophilia center in Kurdistan Province. The study was approved by the ethical committee of Kurdistan University of Medical Sciences. The diagnosis was established based on family history, physical examination, clinical records and coagulation, and platelet function assays. Patients with a history of intake of any drugs affecting platelet function in the previous 4 weeks, with evidence of uremia, liver disease, dysproteinemias, acute leukemia, myeloproliferative disorders, and the myelodysplastic syndrome were excluded. Ethics Committee of Kurdistan University of Medical Sciences approved the study. Written consent was given from all patients or their parents.

Study protocols

At the beginning, all patients were evaluated by routine tests including platelet count (Sysmex kx_21 hematology analyzer, Kobe, Japan), bleeding time (BT-modified Ivy's method, normal range:3-8 minute), prothrombin time (PT, normal range 10-12 seconds) with mixing studies, activated partial thromboplastin time (APTT, normal range 26-40 seconds) with mixing studies (Diagnostica Stago France kits, semi-automatic coagulation analyzer, STAGO, STart®). In the cases with normal coagulation tests, the clot solubility test in 5 M urea or 1 % monochloroacetic acid environment was performed. Patients with the abnormal results of any of these tests, candidate for specific diagnostic assays. Plasma factor activity of coagulation factor was assayed by semi-automated coagulometer (ST-Art Diagnostica Stago, France). The severity of factor deficiencies were categorized according to the level of the specific factors obtained by factor assays (Table1). Von Willebrand factor (vWF) antigen and activity were evaluated by an ACL9000 analyzer (detection limit: 3.5%). Patients with undetectable levels of vWF considered as vWD type III. Platelet aggregation studies using platelet-rich plasma)PRP(with agonists such as ADP (final concentration of 20mol L/1), epinephrine (500 µmol /L), arachidonic acid (500 µg/ L), collagen (10 µg/ L), and ristocetin (1.5 µg/ L) were performed using turbidometric aggregometer (Pack 4, Helena Laboratories, Beaumont, TX, USA). Flow cytometric analysis for glycoprotein receptors on platelets, i.e. GpIIb-IIIa were performed (Partec-pasll, Germany).

Results

Among all investigated patients, 107 patients had different types of CBDs. HA with 60 cases (56%) was the most common bleeding disorder in the province. Among RBDs, FVIID with 64% frequency followed by FVD with a prevalence of 16% were the most common RBDs. Inhibitor screening in cases with an unsatisfactory response to replacement therapy showed only one case with HA developed an inhibitor. Among all patients, two cases affected by HA and vWD simultaneously. Out of 95 patients with coagulation disorders, 53.6%, 15.7% and 12.6% affected by the severe, moderate and mild degrees of disorders, respectively. The frequency of coagulation factor deficiencies was summarized in table 2.

A total of 9 patients with vWD were identified. Out of these 9 patients, 1 of them diagnosed vWD type III and others had vWD type I. Considering inherited platelet disorders, 2 patients had type I Glanzmann thrombasthenia (GT). In one case of platelet disorders, it could not be classified in a specific group. By considering the estimated population of Kurdistan province (1.5 million), the prevalence of HA and HB was 4 and 0.6 in 100000 males, respectively. The frequency of RBDs and platelet disorders was

Table 1: Demographic data of patients before surgery.

Factor	Coagulation factor activity		
	Severe	**Moderate**	**Mild**
I	Undetectable clot	0.1-1g/L	>1g/L
V	Undetectable activity	≤10%	>10%
VII	<10%	10-20%	>20%
VIII	<1%	1-5%	>5%
IX	<1%	1-5%	>5%
X	<10%	10-40%	>40%
XIII	Abnormal clot solubility test	-	-

Table 2: Prevalence of inherited coagulation factor deficiencies.

Disorders	Mild; n (%)	Moderate; n (%)	Severe; n (%)	Not available; n (%)	Total
Common bleeding disorders					
HA	7(11.5)	9(15.5)	41(68)	3(5)	60
HB	-	3(30)	4(40)	3(30)	10
Rare bleeding disorders					
FID	-	-	-	2(100)	2
FVD	1(25)	1(25)	1(25)	1(25)	4
FVIID	4(25)	2(12.5)	4(25)	6(37.5)	16
FXD	-	-	-	1(100)	1
FXID	-	-	-	1(100)	1
FXIIID	-	-	1(100)	-	1

N: Number, HA: Hemophilia A, HB: Hemophilia B, FID: Fibrinogen deficiency, FVD: Factor V deficiency, FVIID: Factor VII deficiency, FXD: Factor X deficiency, FXIID: Factor XII deficiency, FXIIID: Factor XIII deficiency.

calculated 1.73 and 0.8 in 100000 residents.

Discussion

The incidence of CBDs based on countries and ethnicity is different. Iran as a Middle Eastern country has a high rate of parental consanguinity, which results in increased frequency of inherited hemorrhagic disorders. Although the wide spectrum of studies conducted in this country, the exact distribution of these disorders has not established in all parts of the

country. Among different provinces in Iran, Sistan and Baluchestan, southeast of Iran have the highest incidence of CBDs in Iran and most of the reports from Iran focus on this province. Based on the survey in 2014 conducted by WFH in 107 countries, 176,211 people with hemophilia (A and B) were identified. Iran, with 5,369 patients, has the ninth-largest hemophilia population (4,438 had HA and 931 had HB) (4). The number of patients with HA and HB in this study was 60 and 10, respectively which compared to another report from Kurdistan province (Sanandaj city) has lower HA but higher HB patients (HA: 104 cases, HB: no case) (5).

In a study conducted in Khorasan Razavi Province, 287 HA and 92 HB were reported. The prevalence of HA and HB in Khorasan Razavi Province was 10.29 per 100,000 and 3.30 per 100,000 males, respectively which compared with the frequency of disease in the current study is much higher (6-8). Based on Dorgalaleh et al study, it seems the majority of patients registered in the hemophilia center of Tehran but the exact origin of them was not reported (8). Reported prevalence form Tehran Province, is 14 per 100 000 and 2.5 per 100 000 males of HA and HB, respectively (6). In the study conducted in South of Iran, 326 and 46 patients with HA and HB were reported, respectively. On this study, the prevalence of HA and HB was calculated as 7.2 and 1 per 100000 residents (9). Most HA and HB patients had a severe form of the disease, including 68% for HA and 40% for HB. The findings of other studies from Iran are consistent with our study. In this report, the most common RBD is FVIID which is consistent with finding Karimi's in 2009 (9). In the study conducted in 2004 which investigated 750 Iranian patients with RDBs, Mannuci et al also reported FVIID as the most common RBD in Iran (10). These findings were different from reports of RBDs in the south east of Iran.

According to different studies, Iran with about 600 patients with FXIIID is the hotspot of disorder worldwide and southeast Iran had more than 400 patients with this disorder but in the present study, only one case affected by FXIIID is diagnosed. This high frequency of FXIIID in southeast Iran makes this disorder the most common RBDs in Iran (11). FVD was the second RBDs in this study, which accounted for 15% of RBDs. This finding was similar to the report of Mansouritorghabeh et al from the North-Eastern of Iran which report FVD as a second common RBD in this region (7).

In a report from Southern and Southeast of Iran, FVD is fifth and third RBDs, respectively (9, 12). A total of 9 patients had vWD and 2 and GT which was comparable with the result from the South of Iran. In that study on 55 patients, 41.8% affected by GT, 27.2% had Bernard Soulier Syndrome and the remaining had other platelet disorders (9). The study from North-Eastern of Iran reported total of 88 cases with platelet disorders including 50 individuals (56.8%) with vWD and 38 (43.2%) with other platelet disorders (7).

Conclusion

Overall, due to the lack of diagnostic facilities and insufficient awareness of CBDs in developing countries in which governmental resources are restricted, health legislators need accurate data on prevalence and numbers of patients to plan and allot their budgets. Therefore determination the pattern, prevalence and distribution of various CBDs in countries, help ascertainment of global scenario of these type of disorders and important for health care planning and resource allocation.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

References

1. Kizilocak H, Yukhtman CL, Marquez-Casas E, Lee J, Donkin J, Young G. Management of perioperative hemostasis in a severe hemophilia A patient with inhibitors on emicizumab using global hemostasis assays. Ther Adv Hematol. 2019 Jun 27;10:2040620719860025.

2. James P, Salomon O, Mikovic D, Peyvandi F. Rare bleeding disorders - bleeding assessment tools, laboratory aspects and phenotype and therapy of FXI deficiency. Haemophilia. 2014: Suppl 4:71-5.

3. Dorgalaleh A, Tabibian S, Shamsizadeh M. Inherited Platelet Function Disorders (IPFDs). Clin Lab. 2017;63(1):1-13.

4. Eshghi P, Mahdavi-Mazdeh M, Karimi M, Aghighi M. Haemophilia in the developing countries: the Iranian experience. Arch

Med Sci. 2010 Mar 1;6(1):83-9.
5. Kumar S, Sinha S, Bharti A, Meena LP, Gupta V, Shukla J. A study to determine the prevalence, clinical profile and incidence of formation of inhibitors in patients of hemophilia in North Eastern part of India. J Family Med Prim Care. 2019;8(7):2463-2467.
6. Mehdizadeh M, Kardoost M, Zamani G, Baghaeepour MR, Sadeghian K, Pourhoseingholi MA. Occurrence of haemophilia in Iran. Haemophilia. 2009;15(1):348-51.
7. Mansouritorghabeh H, Manavifar L, Banihashem A, Modaresi A, Shirdel A, Shahroudian M, Shoja-E-Razavi G, Pousti H, Esmaily H.. An investigation of the spectrum of common and rare inherited coagulation disorders in north-eastern Iran. Blood Transfus. 2013;11(2):233-40.
8. Dorgalaleh A, Dadashizadeh G, Bamedi T. Hemophilia in Iran. Hematology. 2016;21(5):300-10.
9. Karimi M, Haghpanah S, Amirhakimi A, Afrasiabi A, Dehbozorgian J, Nasirabady S. Spectrum of CBDs in southern Iran, before and after the establishment of comprehensive coagulation laboratory. Blood Coagul Fibrinolysis. 2009;20(8):642-5.
10. Mannucci PM, Duga S, Peyvandi F. Recessively inherited coagulation disorders. Blood. 2004;104(5):1243-52.
11. Dorgalaleh A, Alavi SER, Tabibian S, Soori S, Moradi Eh, Bamedi T, Asadi M, Jalalvand M, Shamsizadeh M. Diagnosis, clinical manifestations and management of rare bleeding disorders in Iran. Hematology. 2017;22(4):224-230.
12. Naderi M, Tabibian S, Shamsizadeh M, Dorgalaleh A. Miscarriage and recurrent miscarriage in patients with congenital factor V deficiency: a report of six cases in Iran. Int J Hematol. 2016;103(6):673-5.