CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
http://doi.org/10.5281/zenodo.4390466

Avalable online at: http://www.iajps.com *Research Article*

AUTOSOMAL RECESSIVE INHERITED BLEEDING DISORDERS IN PAKISTAN

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Article Received: October 2020 **Accepted:** November 2020 **Published:** December 2020

Abstract:

Introduction: *Disorders of hemostasis leading to bleeding are quite common. They can be divided into hereditary and acquired with the acquired defects being more common. All can further be compartmentalized into defects of the vasculature, defects of platelets or defects of the coagulation proteins.*

Aims and objective: *The main objective of the study is to find the autosomal recessive inherited bleeding disorders in Pakistan.*

Material and methods: *This cross sectional study was conducted at Health Department Punjab during 2019. In local set-up, patients are usually diagnosed to have a bleeding disorder at primary and secondary health care centers or general clinics. The confirmatory investigations usually include only the platelets count, bleeding time (BT), Prothrombin time (PT) and activated partial thromboplastin time (APTT). Such cases are hence labelled as merely the bleeding disorder patients.*

Results: *Average age was 6.13±2.33 years, males were 304 (70%) and females were 131 (30%). Out of these 435 patients 273 (62.8%) had coagulation factor deficiency. There were 2 females among the 153 patients with X linked inheritance (Factors VIII and IX). Of the remaining 120 patients with autosomal inheritance there were 67 males and 53 females. Eighty one (18.6%) had platelet function defects. There were 45 males and 36 females among the patients. Another 81 (18.6%) had vWF deficiency.*

Conclusion: *It is concluded that Coagulation factor deficiencies with factor VIII deficiency being the commonest are the most frequent bleeding disorders. Platelet function defects and vWF deficiency also comprise significant proportion of the bleeding disorders.*

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Please cite this article in press Javeria Anwar et al, ***Autosomal Recessive Inherited Bleeding Disorders In Pakistan.,*** *Indo Am. J. P. Sci, 2020; 07(12).*

INTRODUCTION:

Disorders of hemostasis leading to bleeding are quite common. They can be divided into hereditary and acquired with the acquired defects being more common. All can further be compartmentalized into defects of the vasculature, defects of platelets or defects of the coagulation proteins. Although many are forthright, still many particularly the acquired defects may be multifaceted and quite complex with respect to pathophysiology, diagnosis and management1. Vasculature defects are common but often unappreciated causes of bleeding [1]. Patients typically complain of mild to moderate mucosal membrane bleeding and dependent petechiae found on the extremities and usually absent from the torso.

The prevalence of some of these disorders in the local population has only been reported in a few studies and a lack of diagnostic facilities and expertise has prevented a comprehensive study to identify ARBDs [2]. The ARBDs include deficiencies of clotting factors I, II, V, VII, X, XI, XIII, vitamin K-dependent clotting factors [VKDCF; II, VII, IX and X], combined factors V and VIII, von Willebrand disease type 3 (vWD), Glanzmann's thrombasthenia (GT) and Bernard–Soulier syndrome (BSS). The presentation and bleeding pattern in these patients varies according to the etiology of each disorder. Life threatening bleeding episodes e.g., central nervous system or musculoskeletal bleeding, occur rarely [3].

Fibrinogen deficiency has a prevalence of 1 in a million. It is subdivided into two distinct phenotypes: quantitative defect (afibrinogenemia and hypofibrinogenemia) and qualitative defect (dysfibrinogenemia and hypodysfibrinogenemia), Prothrombin deficiency (PD) has a prevalence of approximately 1 in two million and has two phenotypes: true hypoprothrombinemia (type I deficiency) and dysprothrombinemia (type II deficiency). Factor V [FV] deficiency is manifested by skin and mucus membrane bleeding, epistaxis and menorrhagia [4]. Prevalence is 1 in a million. Factor VII deficiency presents as a hemophilia-like bleeding disorder with an estimated prevalence of 1 in 300,000–500,000. The most severe form of vWD is type 3, characterized by a bleeding disorder associated with a total or near-total absence of von Willebrand factor (vWF) with deficiency of plasmatic factor VIII (FVIII). The type 3 vW disease is the rarest form of vWD, accounting for less than 5% of all cases of bleeding disorders worldwide. Annual incidence ranges from 1 in two million to 1 in 350,000 in Europe and the United States, with estimates of around 1 per 500,000 in countries where consanguinity is more frequent. Combined deficiency of factor V and VIII is associated with mutations in the LMAN1 and MCFD2 genes [5].

Aims and objective:

The main objective of the study is to find the autosomal recessive inherited bleeding disorders in Pakistan.

MATERIAL AND METHODS:

This cross sectional study was conducted at Health Department Punjab during 2019. In local set-up, patients are usually diagnosed to have a bleeding disorder at primary and secondary health care centers or general clinics. The confirmatory investigations usually include only the platelets count, bleeding time (BT), Prothrombin time (PT) and activated partial thromboplastin time (APTT). Such cases are hence labelled as merely the bleeding disorder patients. At their visit, patients were enrolled into the current study after acquiring informed written consents. All the non-classified bleeding disorder cases were included into the study. Those categorized as haemophilia A were also included so as to exclude vWD. Patients taking non-steroidal anti-inflammatory drugs (NSAIDS), steroids, clotting factors or those who had had a platelet transfusion 2 weeks prior to the start of the study were excluded.

Biochemical analysis:

Clot solubility test for factor XIII deficiency using 30% urea solution was also put up for every patient. After clotting patient plasma 3 ml urea solution was added to the test tube and the clot dislodged. After 24 hours test tube was inspected for clot dissolution. Clot dissolution indicated factor XIII deficiency.

Statistical analysis:

Data was analyzed using SPSS version 19. Descriptive statistics were used to describe the data i.e mean and standard deviation (SD) for quantitative variables and frequency along with percentage for qualitative variables.

RESULTS:

Average age was 6.13±2.33 years, males were 304 (70%) and females were 131 (30%). Out of these 435 patients 273 (62.8%) had coagulation factor deficiency. There were 2 females among the 153 patients with X linked inheritance (Factors VIII and IX). Of the remaining 120 patients with autosomal inheritance there were 67 males and 53 females. Eighty one (18.6%) had platelet function defects. There were 45 males and 36 females among the patients. Another 81 (18.6%) had vWF deficiency.

There were 41 males and 40 females among the patients. Among the 273 coagulation factor deficiency patients, inherited coagulation factor deficiencies including factor VIII deficiency in 121 (44.3%), factor IX deficiency in 32 (11.7%), factor V deficiency in 18 (6.6%), factor XIII deficiency in 15 (5.5%), factor VII deficiency 12 (4.4%), factor X deficiency 9 (3.3%), factor I deficiency in 8 (2.9%), factor II deficiency in 3 (1.1%). Acquired deficiency in the form of multiple factor deficiency was seen in 55 (20.1%) mainly due to vitamin K deficiency and liver disease.

Table 01: Frequency of various bleeding disorders in Pakista

Bleeding disorder	Frequency	Percentage
Factor VIII deficiency	121	44.3%
Factor IX deficiency	32	11.7%
Factor V deficiency	18	6.6%
Factor XIII deficiency	15	5.5%
Factor VII deficiency	12	4.4%
Factor X deficiency	9	3.3%
Factor I deficiency	8	2.9%
Factor II deficiency	3	1.1%
Multiple factor deficiency	55	20.2%

DISCUSSION:

vWD is the second most common bleeding disorder diagnosed at AFIP Rwp along with platelet function defects. El-Bostany et al documented vWD as the commonest bleeding disorder followed by factor VIII deficiency and platelet dysfunction. Platelet function defects were also documented as the second most common bleeding disorders by Gupta et al and Karimi et al., Only the combination of increased BT and prolonged APTT were taken as evidence of vWF deficiency. No attempt was made to subtype vWD and vWF:Ag and Ricof activity were not measured. Similarly vWF:F VIII binding assay was not done to rule out type 2N vWD. BT of more than 11 min was taken as evidence for platelet function defec [6]t. No distinction was made between inherited and acquired defects. Multiple factor deficiency was the next most common cause of bleeding diathesis. As inherited combined factor deficiencies are quite rare, it probably represents the acquired deficiencies secondary to vitamin K deficiency especially in the newborns or liver disease mainly in the adults [7]. No attempt was made to identify the underlying cause.

Among other coagulation factor deficiencies factor IX deficiency was the second most common after factor VIII deficiency. Next in frequency was deficiency of factor V, factor XIII, factor VII, factor X and factor I. Least frequent bleeding disorder was factor II deficiency. No patient with factor XI deficiency was detected indicating extremely low incidence. In contrast factor XI deficiency has the highest frequency other than hemophilia A and B excluding vWD in UK and Italy [8]. Rare inherited coagulopathies other than factor VIII and IX deficiencies found in our population by Khalid S et al include deficiency of factor VII, factor X, factor XIII, factor V, factor I, factor II and factor XII in the descending order of frequency. Rare inherited coagulation disorders in Southern Iran include factor X, factor VII, factor XIII, factor I and factor XI deficiency in the descending order of frequency whereas from India it is factor X deficiency followed by factor XIII, I, VII and V in the same order. The non sex linked bleeding disorders also demonstrate a slight male predominance [9].

CONCLUSION:

It is concluded that Coagulation factor deficiencies with factor VIII deficiency being the commonest are

the most frequent bleeding disorders. Platelet function defects and vWF deficiency also comprise significant proportion of the bleeding disorders.

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