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ORIGINAL ARTICLE

Frequency of Rare Bleeding Disorders

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ABSTRACT

Objective: The incidence and range of rare hereditary bleeding diseases, as well as the severity of the deficiency and its many clinical presentations, were the subjects of our study.

Study Design: Cross-sectional study

Place and Duration: Department of Pathology, Northwest School of Medicine Peshawar in the duration from July, 2022 to December, 2022.

Methods: Total 850 cases of coagulation disorders were presented in this study. A thorough demographic analysis of the recruited cases was done after receiving informed written consent. After taking note of the symptoms and indicators, a coagulation profile was used to diagnose the patients. With the use of factor tests, the illness severity was evaluated. All of the data was examined using SPSS 23.0.

Results: Among 850 cases, 113 (13.3%) patients were had rare bleeding disorders. In 113 cases of rare bleeding disorders, there were majority 70 (61.9%) males and 43 (38.1%) patients were females. Mean age of the cases was 10.5±13.69 years. 47 (41.6%) cases were from urban areas and 66 (58.4%) cases had rural residency. Most common deficiency was factor VII found in 33 (29.2%) cases followed by fibrinogen in 22 (19.5%) cases. 17 (15.04%) cases had family history of rare bleeding. Frequency of consanguinity was found in 88 (77.9%) cases. Most common clinical symptom was bruising, gum bleeding, epistaxis and menorrhagia.

Conclusion: We concluded higher frequency of rare bleeding disorders in 13.3% cases. Factor VII deficiency is the most typical uncommon bleeding condition in our community. Due to the high rate of consanguineous marriages in our society, these bleeding diseases are very common.

Keywords: Factor deficiency, Rare bleeding disorders, Factor assay, Consanguinity

INTRODUCTION

A complex group of inherited coagulation abnormalities known as uncommon bleeding illnesses include von Willebrand illness, a factor VIII or factor IX deficiency, and deficiencies in fibrinogen, prothrombin, factor V, component VII, factor X, or factor XIII. There are also a few unusual combination factor deficiencies mentioned in it, including combined factor V & VIII insufficiency [1].

Comparatively to other causes of bleeding, the frequency of rare bleeding diseases is uncommonly low at roughly 3-5% [1,2]. However, these disorders are more prevalent in places where consanguineous unions are favored [3]. Such unions are common in Pakistan [3]. A thorough investigation to detect ARBDs has been hindered by a lack of diagnostic resources and experience, as well as the rarity of some of these illnesses in the local community, as documented in just a few studies [4].

The ARBDs include the following: von Willebrand disease form 3 (vWD), Glanzmann's thrombasthenia (GT), Bernard-Soulier syndrome (BSS), vitamins K-dependent coagulation factors II, VII, IX, and X, combining factors V and VIII, and clotting factor deficiencies I, II, V, VII, X, XI, and XIII. The appearances and bleeding patterns of these people vary depending on the etiology of each illness [5,6]. A life-threatening bleeding event such a musculoskeletal or central nervous system hemorrhage happens seldom.

Fibrinogen insufficiency affects one in a million people [7]. Prothrombin deficiencies (PD) have two distinct phenotypes: true low level (type I disfunction) and dysprothrombinemia (also known as the kind II deficiency), which have been classified as numerical imperfections (afibrinogenemia as well as hypofibrinogenemia) as well as personal flaws (dysfibrinogenemia and hypodysfibrinogenemia) [8]. The prevalence of PD is about 1 in 2 million people. Menorrhagia, epistaxis, and skin or mucous membrane bleeding are signs of factor V [FV] deficiency. It affects one person in a million. Factor VII deficiency presents as a bleeding disorder comparable to hemophilia and is thought to occur between 1 in 300,000 and 500,000 people [9]. Von Willebrand disease (vWD) type 3 is the most severe kind and is characterized by a bleeding disorder, a total or almost complete loss of von Willebrand factor (vWF), and a deficiency of plasmatic factor VIII (FVIII). kind 3 vWD individuals make up the rarest kind of vWD, accounting for less than 5% of all cases of bleeding disorders worldwide. In countries where consanguinity is permitted, the incidence varies from 1 in 2 million to 1 in 350,000 annually, compared to an estimated frequency of 1 per 500,000 in Europe and the US. The LMAN1 and MCFD2 genes have mutations that are related to combined factor V and VIII deficiency [10]. It is distinguished by concurrently low levels (often between 5 and 20%) of both FV and FVIII and is linked to a mild to moderate propensity to hemorrhage [11,12].

These illnesses stand out because they are uncommon in the general population and exhibit a wide range of clinical manifestations [13]. Data on the prevalence of these uncommon bleeding diseases in underdeveloped nations, including Pakistan, are currently unavailable. Despite the low occurrence of these illnesses worldwide, they are underdiagnosed and underreported in underdeveloped nations. This can be because there aren't enough diagnostic resources available for advanced diagnostics like factor assays. Since the prevalence of these disorders in our population is unknown, there is little public awareness of them and little clinical suspicion of them, which results in many missed cases.

Although uncommon, these disorders can cause significant bleeding, so it's crucial to get a timely diagnosis in order to make the best treatment choice. Depending on the kind of factor deficit, there are many treatment options [14]. Factor concentrates are used to accomplish definitive replacement treatment, but their availability is restricted in nations with poor resources, and even when they are, their exorbitant cost is a serious issue. These factors may force doctors to treat these patients with fresh-frozen plasma (FFP) and cryoprecipitate. It is crucial to get the right diagnosis before choosing a treatment, whether it be a plasma product or a concentrated form of a certain factor [15].

Diagnostic facilities are lacking in Pakistan, a developing nation with little resources. In-depth information on the prevalence of these uncommon bleeding diseases in this nation is what the current study's design aims to give. This study was carried out to characterize the pattern of these bleeding diseases, the clinical manifestations of these patients, and the care given to these patients who visited our center. The results of the study will be valuable in creating a database of these uncommon bleeding diseases in our community, which will aid physicians in making an early diagnosis and determining the best course of therapy.

MATERIALS AND METHODS

This cross-sectional study was conducted at Department of Pathology, Northwest School of Medicine Peshawar in the duration from July, 2022 to December, 2022 and comprised of 850 cases of coagulation disorders. A thorough demographic analysis of the recruited cases was done after receiving informed written consent. Patients having acquired coagulation problems, including disorders of platelet function, were disqualified from the research.

Patients that were included ranged in age from 5 months to 45 years. A bleeding history or a possible hereditary clotting disease should be considered in every patient. We noticed some demographic information. A thorough history was collected, including information on the patient's past and present bleeding history, bleeding sites, the number of episodes of bleeding, family history, consanguinity, treatment history, and transfusion history. A clinical exam was done, paying close attention to look for any bruises or petechiae. It was mentioned the symptoms and indications. To exclude any liver disease that could have an impact on the coagulation profile, liver function tests were performed.

Using the Sysmex XE-5000 automatic hematological cell count (Sysmex Corporation, Kobe, Japan), complete blood counts were carried out on a two-milliliter amount of venous blood drawn and stored in EDTA. Ivy used her method to bleed time. For coagulation testing, venous blood was collected and put in a trisodium citrate 9:1 solution. The accelerated partial thromboplastin time (also known as and prothrombin time (PT) tests were performed first on an automated clotting analyzer CA-1500 (Sysmex, Kobe, Japan). The usual control values were 11 and 25, respectively, for PT and aPTT. The manual measurement of thrombin time was carried out using the Montana thrombin time reagent of BD Bioscience in San Jose, Calif., USA. Utilizing a urea clot test for solubility with 5 M urea, factor XIII was assessed. An inhibitor screen was then carried out by combining normal plasma 1:1 with all anomalous findings before they were manually retested utilizing Helena PT or aPTT reagents. The tests were then combined with locally produced adsorbed plasma and aged serum. Specific component tests were conducted in response to the results using the CA-1500 automatic hematological analyzer. An aPTT-based factor assay was used to test factors VIII, IX, XI, and XII, whereas factors V, VII, and X were evaluated using a PT-based component assay. Both tests were performed on plasma deficient in Siemens factor. The manufacturer's instructions state that the standard deviations used for factor testing for aPTT-based assays should be between 70 and 150%.

The data was input and analysed using IBM SPSS software 23. The average and standard deviation (meanSD) of quantitative data were presented, including the frequency and percentage of categorical variables. To compare the baseline characteristics, the chi-square test was used. Each P-value has two faces to it. If P 0.05, statistics were considered significant.

RESULTS

Among 850 cases, 113 (13.3%) patients were had rare bleeding disorders.(figure 1)

In 113 cases of rare bleeding disorders, there were majority 70 (61.9%) males and 43 (38.1%) patients were females. Mean age of the cases was 10.5±13.69 years. 47 (41.6%) cases were from urban areas and 66 (58.4%) cases had rural residency.(table 1)

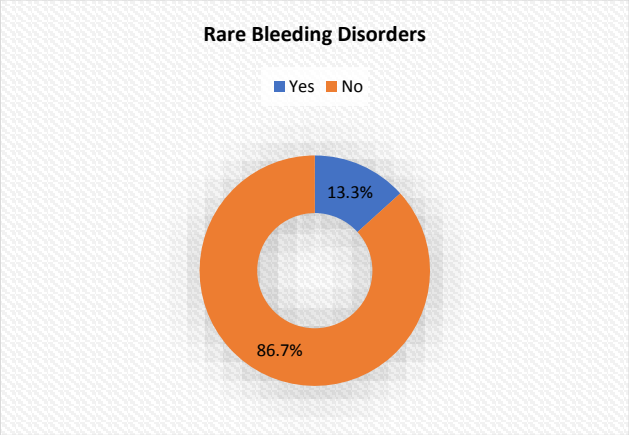

Figure-1: Frequency of rare bleeding disorders

Table-1: Demographics of the RBD patients

Variables	Frequency	Percentage
Mean age (years)	10.5±13.69	
Gender		
Male	70	61.9
Female	43	38.1
Place of Living		
Rural	47	41.6
Urban	66	58.4

Seventeen (15.04%) cases had family history of rare bleeding. Frequency of consanguinity was found in 88 (77.9%) cases.(table 2)

Table-2: Family history and consanguinity among RBD patients

Variables	Frequency	Percentage
Family history of RBD		
Yes	17	15.04
No	96	94.96
Consanguinity		
Yes	88	77.9
No	25	22.1

Most common deficiency was factor VII found in 33 (29.2%) cases followed by fibrinogen in 22 (19.5%) cases.(figure 2)

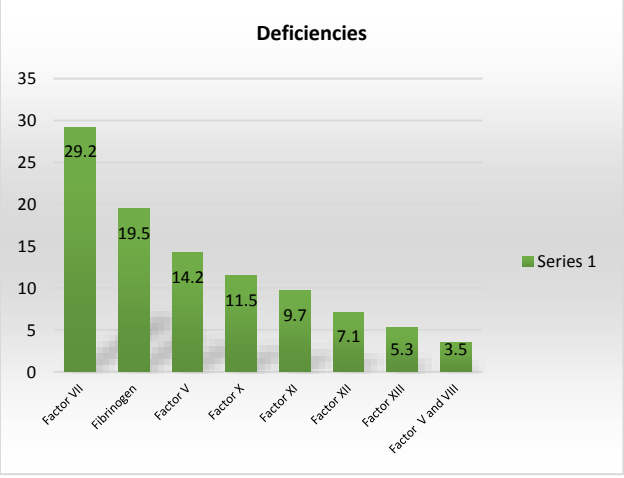

Figure-2: Types of rare bleeding disorders

Most common clinical symptom was bruising, gum bleeding, epistaxis and menorrhagia.(table 3)

Table-3: The clinical characteristics of people with rare bleeding diseases

Variables	Frequency (113)	Percentage
Symptoms		
bruising	72	63.7
gum bleeding	60	53.1
epistaxis	48	42.5
menorrhagia	37	32.7
Post circumcision bleed	24	21.2
Umbilical stump bleed	16	14.2
PPH	13	11.5
Post-operative bleed	11	9.7
CNC bleed	9	7.96
Gastrointestinal bleed	5	4.4

DISCUSSION

Advanced treatment options are becoming available in industrialized nations as more is known about the incidence of these illnesses, their clinical manifestations, and management tactics. The therapy of patients with uncommon bleeding diseases has, however, been significantly hampered in developing nations with limited resources due to the delay in diagnosis and the inadequate availability of therapeutic modalities. The creation of a register for our population is necessary given the biological diversity and regional differences in disease manifestation and severity. The creation of a database for our population is crucial for the prompt identification of these patients as well as the creation of clinical treatment recommendations that are suitable for our setup and resources.

In current study 850 cases were presented. Among 850 cases, 113 (13.3%) patients were had rare bleeding disorders. A frequency of 15.6% was noted in the Iranian population, according to Mansouritorghabeh et al. [16]. Factor VII insufficiency (29.2%) and fibrinogen deficit (19.5%) were the two uncommon bleeding disorders that affected our group most often. Factor X deficiency was shown to be the second-most common uncommon bleeding illness, according to a study done at the Fars Hemophilia Center, a part of Shiraz University of Medical Sciences in Iran [17]. Factor X deficiency, followed by factor XIII and factor VII deficits, was listed by Sharma et al. [18] as the most prevalent uncommon bleeding condition. Factor VII and V deficits were shown to be the most prevalent uncommon bleeding diseases in a retrospective examination of 156 individuals in Turkey [19].

Most common clinical symptom was bruising 63.7%, gum bleeding 53.1%, epistaxis 42.5% and menorrhagia 32.7%. Gum bleeding was more noticeable in people with Glanzmann thromboasthenia and Bernard-Soulier syndrome, hemarthrosis was more prevalent in people with factor VII deficiency, and hematoma was more obvious in people with factor XIII, factor V, and vitamin K dependent clotting factor deficiency. The most frequent cause of protracted umbilical cord hemorrhage in patients was factor XIII insufficiency. Factor VII and vitamin K dependent clotting factor deficiencies, GT, and BSS were linked to prolonged bleeding after trauma. A prior study found that factor XI, BSS, and GT deficiencies are all characterized by easy bruising.[20]

In our study, seventeen (15.04%) cases had family history of rare bleeding. Frequency of consanguinity was found in 88 (77.9%) cases. South Asian countries, particularly Pakistan, have a high frequency of consanguineous partnerships [21], which explains the increased prevalence of ARBD in this region.[22] Sharma et al.'s [23] findings were comparable. Patients with factor X deficiency in our group had clinically substantial bleeding. Two individuals with factor X deficiency, one with factor VII and the other with factor XIII, both of whom had intracranial hemorrhage, were seen. However, a study conducted in India found that factor XIII deficiency was the most typical reason for intracranial bleeding [23]. However, the only patients in our study were those who were referred to us or who presented to the hospital. Many people who reside in rural regions and do not have access to tertiary care diagnostic facilities go undetected. This means that the prevalence of these bleeding problems in our community may be substantially higher than is often believed. Due to Pakistan's limited resources and the lack of a facility for the molecular diagnosis of RBDs, the diagnosis of rare blood diseases (RBDs) was made only based on the findings of coagulation tests in this study, which has the drawback of not include molecular genetic investigations.[24]

CONCLUSION

We concluded higher frequency of rare bleeding disorders in 13.3% cases. Factor VII deficiency is the most typical uncommon bleeding condition in our community. Due to the high rate of consanguineous marriages in our society, these bleeding diseases are very common.

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