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Epidemiological Profile of Patients with Hemophilia in Northern Pakistan; A One-Center Study

Lubna Zafar [1], Tahira Zafar [2] Usama Azam [3], Asma Nafisa[4] Sundas Durrani [5], Mehwish Iqbal [6] Nadeem Ikram [7]

[1]Department of Pathology, Foundation Medical College, [2]Haemophilia Patients' Welfare Society, Rawalpindi, [3]Department of Pathology, Benazir Bhutto Hospital, Rawalpindi, [4]Department of Pathology, Benazir Bhutto Hospital, Rawalpindi; [5]Department of Pathology District Head Quarters Hospital, Rawalpindi, [6]Department of Pathology, Rawalpindi Medical College, [7]Department of Pathology, Akhtar Saeed Medical College, Rawalpindi

Address for Correspondence
Dr. Lubna Zafar
lubnazafar2008@hotmail.com

Abstract

Objective: To study the epidemiological profile of patients with haemophilia in northern Pakistan.
Methodology: This research was cross-sectional and observational. Investigations were conducted on hemophiliac patients of various ages who had registered with the Hemophilia Patients Welfare Society in Rawalpindi. A thorough clinical and epidemiological history was gathered from the patient or the patient's accompanying parent or guardian using a pre-structured questionnaire. In accordance with test results and factor VIII and IX assay levels, patients were further divided into mild, moderate, and severe groups.
Results: One female patient of Hemophilia B is one of the important findings of this study. Out of total 837 patients investigated, 702 were of Hemophilia A and 135 were of Hemophilia B. 46.47% (389/837) belongs to the age group of >17 years. 476 (56.86%) were severe hemophiliacs, 269 (32.15%) were moderate and 92 (bn 10.99%) were mild hemophilia patients. Knee was the most involved joint and it was observed in 331 (39.57%) patients.
Conclusion: The most common type of hemophilia is the severe form of hemophilia a (classic hemophilia). This study also found a female hemophilia B case which is the novel identification of this study. It is concluded that there is a need to start a national level diagnosis, prevention and care program for hemophilia patients.
Keywords: Hemophilia, bleeding, congenital, x-chromosome, knee joint.

Introduction

Inherited bleeding disorders are a type of coagulation diseases which are caused due to the deficiency or abnormal function of the plasma proteins which helps in normal clotting.[1] Von Willebrand and hemophilia are considered most common type of HBDs. [2] Hemophilia is of three types and is a congenital bleeding disorder linked with x-chromosome and it is caused due to the deficiency of clotting factor VIII (Hemophilia A), factor IX (Hemophilia B) and the third one is the rarest form caused due to deficiency of factor XI (Hemophilia C) and is an autosomal recessive disorder.[3] Hemophilia A is also termed as Classic Hemophilia and it is 5 times more prevalent than hemophilia B which is also called as Christmas disease.[4] These two are the only HBDs that are inherited in a sex-linked form and the afflicted gene is located on the X-chromosome.[5]

Hemophilia is speculated in person who has a history of bruising, longer clotting time after cuts, spontaneous bleeds in soft tissues, muscular tissues and joints and post traumatic severe bleeding.[6] The probability of spontaneous and an early age bleeding episode increases in patients with more severe hemophilia.[7] In infants, mostly affected sites are brain, CNS and also bleed more after medical procedures of circumcision, venipunctures.[8] In grown up children, mostly joints and muscles are affected.[9] Lack of treatment leads to early death of severe hemophiliacs, however, in today's world, the advanced level of hemophilia treatment is available and is very effective and has increased the life expectancy of patients with hemophilia.[10]

According to World Federation of Hemophilia's annual global survey 2020, there are about 2,41,535 identified people of all kind of Hemophilia and the expected patients globally are 8,15,100 with a prevalence rates of 24.6/100,000 males for all Hemophilia A patients and 5.0/100,000 males for all Hemophilia B patients.[1] The annual report of World Federation of Hemophilia (WFH) in 2020 revealed that in Pakistan, the total identified number of patients suffering from any type of hemophilia are 2459.[1] However, the true incidence rate of the hemophilia could be higher due to the consanguinity factor, scarce diagnostic resources, and lack of awareness of the disease.[11] The research work on the epidemiology of Hemophilia in Pakistan is very scarce and this study aimed to investigate this perspective and to explore the extent of disease in our patients.

Methodology

The research was conducted in Northern Pakistan at the Hemophilia Care Centre (Hemophilia Patents Welfare Society Rawalpindi). The participants were the 898 individuals who had registered in this hemophilia treatment program. Due to insufficient data, 61 patients were eliminated from the study, leaving an overall sample size of 837. Study design was descriptive and observational. Data was abstracted using a structured data collection form: a. Patient demographics: gender, age, and marital status; b. Patient clinical profile: kind of hemophilia, blood group, and illness severity; d. Family history. A complete history of presentation was taken, including joint involvement for bleeding episodes in the previous year, as well as additional symptoms and consequences episodes (like intracranial haemorrhage) during last one year. Along with that, other complications related with these episodes were also noted. On the basis of factor levels patients were divided into three groups, i.e., mild, moderate and severe.

Inclusion criteria: All patients diagnosed with any type of hemophilia and registered with the Hemophilia treatment center (Hemophilia Patients Welfare Society-Rawalpindi, Pakistan).

Exclusion criteria: Patients with hereditary bleeding disorders other than hemophilia, as well as acquired bleeding disorders due to medications, infections, tumors and platelet problems.

The center's administration and the committee of health research gave their ethical and official authorization. Patients' consent was also obtained. All information was kept private and utilized solely for the purpose of the study

The descriptive analysis of qualitative variables was examined with SPSS and expressed in frequency and percentages in the statistical approach. The mean value was used to get the statistical average, and the standard deviation was used to calculate the dispersion. The Chi - Square test was applied to compare the qualitative variables between two types of Hemophilia

Results

The study included a total of 837 patients, with a predominant male population (99.9%). Only one female patient were within the age groups of 18-44 years (46.6%), while a small percentage (4.5%) were aged 45-100 years.Most patients were unmarried (88.54%). The age at initial diagnosis was primarily less than one year (61.6%), followed by those diagnosed between 1-5 years (29.9%) and those diagnosed after 5 years of age (8.5%) (Table I)

Table I: Clinical and Sociodemographic Features of Patients Registered at Hemophilia Treatment Centre Rawalpindi.

Gender	Number (%)
Male	837(99.9%)
Female	1
Age groups(years)	
0-17	389(46.4)
18-44	403(48.1)
45-100	46(5.37)
Age(undocumented)	30(3.6)
Marital status	
Married	96(11.46)
Unmarried	741(88.54)
Age at initial diagnosis	
<1 year	516(61.6)
1-5 years	250(29.9)
>5 years	71 (08.5)
Hemophilia type	
Hemophilia A	702(83.9)
Hemophilia B	135(16.1)
Severity of hemophilia	
Mild	89(10.6)
Moderate	244(29.1)
Severe	420(50.1)
Family history of hemophilia	506(60.4)
Siblings	233(44.8)
Maternal uncles	157(30.2)
Maternal cousins	130(25.0()
Bleed Type	
Post circumcision bleed	428(51.35)
Cut bleed	144(17.2)
Hemarthrosis	72(8.6)
Bruises or gum bleeds	128(15.3)
Intracranial Hemorrhage	65 (7.76)

Regarding hemophilia types, A was the most common, affecting 83.9% of the patients. In terms of disease severity, half of the patients (50.1%) were diagnosed with severe hemophilia. Various bleeding types were reported, with the most common being post-circumcision bleeding (51.4%), followed by cut bleeds (17.2%), bruises or gum bleeds (15.3%), hemarthrosis (8.6%), and intracranial haemorrhage (7.76%). Table I

The study compared the clinical characteristics between patients with Hemophilia A and Hemophilia B. Regarding disease severity, a significant difference was observed

Table II: Comparison of Clinical Variables in both Groups of Hemophilia Patients.

Clinical variable	Hemophilia A	Hemophilia B	total	χ^2 p=value
Disease Severity				
Mild	65 (9.3)	27 (19.7)	92 (10.99)	36.35 0.0001
Moderate	210 (29.9)	59 (43.7)	269 (32.15)	
severe	427(60.8)	49 (36.29)	476 (56.86)	
Involved joints				
Knee	278 (39.6)	52 (38.51)	331 (39.57)	34.23 0.0001
Shoulder	20 (2.8)	0 (0.00)	20 (2.38)	
Elbow	53 (7.5)	6 (4.4)	59 (7.04)	
Ankle	90 (12.8)	15 (11.3)	106 (12.66)	
Other joints or soft tissues, muscles	261 (37.2)	60 (45.8)	321 (38.35)	
Disability				
Severe disability	192 (27.4)	25 (19.7)	217 (26.16)	23.44 0.0001
Partial or no disability	510 (22.6)	108 (80.3)	618 (73.84)	

between the two groups (χ^2 = 36.35, p = 0.0001). In patients with Hemophilia A, 9.3% had mild disease, 29.9% had moderate disease, and 60.8% had sever disease. In contrast, among patients with Hemophilia B, 19.7% had mild disease, 43.7% had moderate disease, and 36.29% had severe disease. (Table II)

Joint involvement was another clinical variable assessed, revealing a significant difference (χ^2 = 34.23, p = 0.0001). The most commonly involved joint was the knee, affecting 39.6% of Hemophilia A patients and 38.51% of Hemophilia B patients. Other joint involvements included the shoulder (2.8% in Hemophilia A, 0% in Hemophilia B), the elbow (7.5% in Hemophilia A, 4.4% in Hemophilia B), and the ankle (12.8% in Hemophilia A, 11.3% in Hemophilia B). Other joints or soft tissues were affected in 37.2% of Hemophilia A patients and 45.8% of Hemophilia B patients (Table II). Disability status also differed significantly between the two groups (χ^2 = 23.44, p = 0.0001). Severe disability was present in 27.4% of Hemophilia A patients and 19.7% of Hemophilia B patients. However, partial or no disability was more common in Hemophilia B patients (80.3%) compared to Hemophilia A patients (72.6%). (Table II)

Discussion

In this study, epidemiological and clinical profile of 837 patients diagnosed with hemophilia A (factor VIII deficiency) and B (factor IX deficiency) was observed with respect to the age, gender, family history and clinical presentations including joint involvement. This descriptive study highlighted some important facts. It was noted that 702 (83.9%) patients had Hemophilia A while 135 (16.1%) were suffering from Hemophilia B. Previous research work has also observed that Hemophilia A is more common than Hemophilia B.[12] In the present study, 60.8% of Hemophilia-A and 36.29% of Hemophilia B were severe hemophiliacs, 29.9% of Hemophilia A and 43.7% of Hemophilia B were moderate hemophiliacs and only 9.9% of Hemophilia A and 19.7 of Hemophilia B were mild hemophiliacs. These results can be compared with the results of studies on Bangladeshi people by Rahman et al[12, 13] and two other studies also reported same outcomes.[14, 15] In our study, 45.2% patients belonged to the '1 month to 15 years of age group' while 53.6% were more than 15 years of age

Similar results were reported by few previous studies.[16,17] Most of our patients have severe disease with factor levels less than 1 percent and are diagnosed early i.e. 516 (61.6%) shows initial bleeding indications before the age of 1 year. The most common initial bleeding presentation was post circumcision bleed (51.35%) and the reason behind this is the religious practice of early circumcision and 250 (29.9%) of cases were diagnosed by 5 years of age and only 71 (8.5%) were diagnosed after 5 years of age. These cases diagnosed after 5 years of age are patients having mild to moderate form of hemophilia. Previous studies show that such patients have minimal symptoms and are usually present at a later age.[18]

This study also highlighted the family history pattern i.e. 520 (62.13%) patients show positive family history, whereas the 317 (37.87%) patients show negative family history for hemophilia. These family history findings are similar to those reported in an Iraqi study of Kamal, Faris and Khadim.[4, 19] These findings are comparable with the results of an Indian study on hemophiliacs and a Korean study by Kim and Kir and also a Pakistani study on

clinicohematological spectrum by Nadeem, Khalid et al.[5, 12, 20]

The novel finding of this study is the diagnosis of Hemophilia B (Christmas disease) in female. This female patient was diagnosed at the age of five years and had a factor IX level of 0.013 IU/ml. Her elder brother had Hemophilia B. She was symptomatic since childhood having repetitive bleeding in left knee joint. Girls and women with affected expression of both X-chromosomes often have moderate or severe F-VIII or F-IX deficiencies. This is observed in extremely rare contexts such as homozygous state for a given F8 or F9 gene mutation, a compound heterozygous state where two different mutations are inherited for each parent. A structural or numerical aberration of X-chromosome (such as Turner Syndrome, Swyer Syndrome, translocations), a non-random skewed X-chromosome inactivation (skewed XCI) pattern or an extreme lyonization can also be held responsible.[23-26]

The high proportion of patients diagnosed with severe hemophilia at an early age suggests potential areas for early intervention and improved management strategies. Furthermore, the novel finding of Hemophilia B in a female patient deserves a more thorough exploration, including potential genetic explanations and implications for clinical practice.

The joints involvement ratio found in this study is knee in 331 (39.57%) cases, ankle joint in 106(12.6%) cases, elbow joint in 59(7.04%) cases, shoulder joint in 20 (2.38%) cases and other joints were observed in 321 (38.35%) of cases. Our results are comparable with a study of Nadeem et al.[6] Similar results were also noticed in a Bangladeshi study on hemophiliac children.[22]

Conclusion

Majority of patients had severe Hemophilia. These patients had bleeding manifestations before the age of five. Post circumcision bleed was the most prevalent presenting symptom at the time of diagnosis. Joint bleeding is common, knee joint being the most affected One female patient was diagnosed as Hemophilia B (factor IX deficiency) which is a rare finding. Specific factor replacement therapy is the most readily available and efficient treatment option. A multidisciplinary strategy is required to improve hemophiliac care and early diagnosis, and this includes educating healthcare professionals, establishing care facilities, and upholding appropriate patient registry, offering low-cost factor concentrates, and instructing patients and their families. This research also highlights the necessity of launching a national program for hemophilia right once, which should include elements of diagnosis, prevention, treatment, and support, given that Pakistan does not currently have a national policy on the prevention and control of genetic illnesses.

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