ORIGINAL RESEARCH ARTICLE

Epidemiological Profile of Patients with Hemophilia at Tertiary Care Center of Western Uttar Pradesh

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ABSTRACT

Introduction: Hemophilia is a rare, congenital, chronic and expensive to treat disorder. Hemophilia is not a disease of public health relevance in India because the focus of public health services in India is on the control of highly prevalent communicable diseases. In such circumstances the data collection related to hemophilia acquires very low priority. So this study was undertaken with objectives to describe the epidemiology of hemophilia patients at Government medical college in Western Uttar Pradesh and assess common complications and prevalence of hepatitis B, hepatitis C and HIV in relation to specific replacement therapy.

Material and Methods: This is an observational cross sectional study which included 77 male subjects and are divided into 2 groups: group I (<18 years age) n=26 and group II (>18 years age) n=51. Patients with Hemophilia A and B who visited the hospital for treatment or factor replacement therapy were evaluated. The viral markers tested in these patients included Australia antigen (HBsAg), anti HCV antibody (anti-HCV-Ab), and antibodies against HIV (anti-HIV-Ab).

Results: In our study the ratio of patients with hemophilia A to B in group I and group II was 7.6:1 and 7.5:1 respectively. Family history of hemophilia is present in 69.23% (group I) and in 49.02% (group II) patients. Significant association was found between family history and type of hemophilia in group I patients (*P*=0.005). A total of 77 male hemophiliacs with history of transfusion showed prevalence of 9.09% for Hepatitis-C, 7.35% for Hepatitis-B, and nil for HIV.

Conclusion: Our study shows that hemophilia A is more common disorder than hemophilia B. Most common presenting symptom at the time of diagnosis was soft tissue bleeding and knee joint is the most commonly involved joint. Hepatitis C is the most frequently identified transfusion transmitted viral infection than Hepatitis B and HIV.

Key words: Hemophilia A and B, Hepatitis B and C, HIV- Human Immunodeficiency Virus, Transfusion Transmitted Infections

INTRODUCTION

Hemophilia is an X-linked recessive congenital bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) in hemophilia A or factor IX (FIX) in hemophilia B. Hemophilia C is an autosomal recessive disorder.[1] Hemophilia has an estimated frequency of approximately one in 10,000 births. Estimations based on the WFH's annual global surveys indicate that the number of people with hemophilia in the world is approximately 400,000.[2]

Hemophilia A is more common than hemophilia B, representing 80-85% of the total hemophilia population. Hemophilia generally affects males on the maternal side. However, both *F8* and *F9* genes are prone to new mutations, and as many as one- third of all cases are the result of spontaneous mutation where there is no prior family history. Changes in the *F8* gene are responsible for hemophilia A, while mutations in the *F9* gene cause hemophilia B. Mutations in the *F8* or *F9* gene lead to the production of an abnormal version of coagulation factor VIII or coagulation factor IX, or reduce the amount of one of these proteins.[3-6]

A family history of bleeding is obtained in about two-thirds of all patients. A definitive diagnosis depends on factor assay to demonstrate deficiency of FVIII or FIX. Hemophilia should be suspected in patients presenting with a history of: easy bruising in early childhood; "spontaneous" bleeding (bleeding for no apparent/known reason), particularly into the joints, muscles, and soft tissues; excessive bleeding following trauma or surgery.

It is estimated that 10-80% of patients with hemophilia are present in developing countries such as India.[7] Given the incidence of hemophilia A is one in 5000 and hemophilia B is one in 30000, as in the US, one expects India to have close to 100000 hemophilia patients.[8] In India, a disease registry for hemophilia is available with Hemophilia Federation of India (HFI). This is a Non Governmental Organisation (NGO) collects data on the number of patients through various centers located across India. The data showed that in 2017-2018, India reported: 20099 patients with bleeding disorders and 16823 patients with hemophilia A and 628 patients with hemophilia B.[9] However, hemophilia cases

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remain under-diagnosed, and many cases are not registered.[10] In June 2009, the Government of Uttar Pradesh made anti-hemophilic factors available at few centers. Consequently, the level of hemophilia care has improved considerably in recent times. The treatment has been life-saving and also improved the quality of life of hemophilia patients. This is a milestone in hemophilia management in Uttar Pradesh.[10]

Aims and Objectives

1) To describe the epidemiology of hemophilia patients at tertiary care center in Western Uttar Pradesh and to assess common complications in relation to specific replacement therapy.
2) To estimate the prevalence of transfusion transmitted infections (hepatitis B, hepatitis C, and HIV) in hemophilia patients.

MATERIAL AND METHODS

It is an observational cross sectional study of 18 months duration (Jan 17 to June 18), approved by institutional ethical committee, comprising of already diagnosed or newly diagnosed patients of hemophilia from Western UP who attended/admitted in the Department of Medicine, Pediatrics and orthopedics at S.V.B.P Hospital associated with L. L. R. M. Medical College, Meerut with complications and/or for factor concentrate / FFP transfusion or having history of such type of transfusion. Total number of patients are 77 and divided into two groups i.e., group I (<18 years age) which has 26 patients and group II (>18 years age) having 51 patients. A detailed clinical history was elicited from the patient's accompanying guardian/parent regarding demographic features, presenting symptoms, symptom profile, duration of symptoms, family history, history of previous transfusion and other relevant history along with detailed general physical examination, joint examination, neurological examination and other systemic examination. Grading of severity of hemophilia is done according to factor VIII or IX activity as follows: Mild = >5% factor activity, Moderate =1-5% factor activity and Severe = <1% factor activity. Relevant investigations related to disease as well as investigation associated with transfusion associated infections (Hepatitis-B, Hepatitis-C and HIV 1 and 2) were also done. The viral markers tested in these patients included HBsAg (Australia antigen), anti-HCV-Ab (anti HCV antibody), and anti-HIV-Ab (anti HIV antibody).

STATISTICAL ANALYSIS

Statistical evaluation was performed using the software; Statistical Package of the Social Sciences (SPSS version 13). For qualitative data (frequency and proportion) chi square test was used and for quantitative data mean and SD and median test was used. *P* value<0.05 is considered significant.

RESULTS

In our study a total of 77 patients were enrolled and divided into two groups. In group I there were 26 patients. Out of these (n=26), 88.46% patients had hemophilia A, 11.53% patients had hemophilia B. The ratio of hemophilia A to B is 7.6:1. Various target joint involvement is found in 53.84%

S.N	Clinical feature		Type A Hemophilia (n=23)	Type B Hemophilia (n=3)	Overall (n=26)
1	Severity Of Hemophilia	Mild	0 (0%)	1(33.3%)	7 (26.9%)
		Moderate	6 (26.085%)	1(33.3%)	1 (3.8%)
		Severe	17 (73.91%)	1(33.3%)	18 (69.23%)
2	Family History	Present	18 (78.27%)	0 (0%)	18 (69.23%)
3	Joint Involvement		14 (60.86%)	1 (33.3%)	15(57.69%)
4	Target Joint	Knee	9 (39.13%)	0 (0%)	9 (34.61%)
5	Joint Swelling	Present	13 (56.52%)	1 (33.3%)	14 (53.84%)
6	Joint Movement	Compromised	13 (56.52%)	1 (33.3%)	14 (53.84%)
7	Site of Bleed	Soft Tissue	14 (60.86%)	2 (66.6%)	16(61.53%)
		Joint Bleed	2 (8.695%)	0 (0%)	2 (7.69%)

Table-1: Summary of clinical features of group I hemophilia patients

S.N	Clinical features		Type A Hemophilia (n=45)	Type B Hemophilia (n=6)	Overall (n=51)
1	Severity Of Hemophilia	Mild	1(2.22%)	1(16.66%)	2(3.9%)
		Moderate	3(6.66%)	2 (33.3%)	5(9.8%)
		Severe	41 (91.11%)	3 (50%)	44(86.27%)
2	Family History	Present	23 (51.11%)	2 (33.3%)	25 (49.02%)
3	Joint Involvement		41 (91.11%)	4 (66.6%)	45 (88.23%)
4	Target Joint	Knee	33 (73.33%)	2 (33.3%)	35(68.62%)
5	Joint Swelling	Present	41(91.11%)	4 (66.6%)	45(88.23%)
6	Joint Movement	Compromised	41(91.11%)	4 (66.6%)	45(88.23%)
7	Site of Bleed	Soft Tissue	30(66.66%)	2 (33.3%)	32(62.74%)
		Joint Bleed	8 (17.77%)	2 (33.3%)	10(19.60%)

Table-2: Summary of clinical features of group II hemophilia patients

Family history	Type of Hemophilia		Overall, (n=26)	Chi square, (*p* value)
	Type A Hemophilia (n=23)	Type B Hemophilia (n=3)		
Absent	5(21.73%)	3(100%)	8(30.76%)	0.005
Present	18(78.26%)	0(0%)	18(69.23%)	

Table-3: Association between family history and type of hemophilia in group I patients

Family history	Type of hemophilia		Overall, (N=51)	Chi square, (*p* value)
	Type A Hemophilia (N=45)	Type B Hemophilia (N=6)		
Absent	22(48.889%)	4(66.66%)	26(50.98%)	0.41
Present	23(51.11%)	2(33.33%)	25(49.02%)	

Table-4: Association between family history and type of hemophilia in group II patients

Transmitted Infection	Type A (n=68)	Type B (n=9)	Total (n=77)
Hepatitis B	4(5.88%)	1(11.11%)	5 (6.49%)
Hepatitis C	5(7.35%)	2 (22.22%)	7(9.09%)
HIV 1 and 2	0(0%)	0 (0%)	0(0%)

Table-5: Prevalence of Hepatitis-B, Hepatitis-C and HIV in hemophilia patients

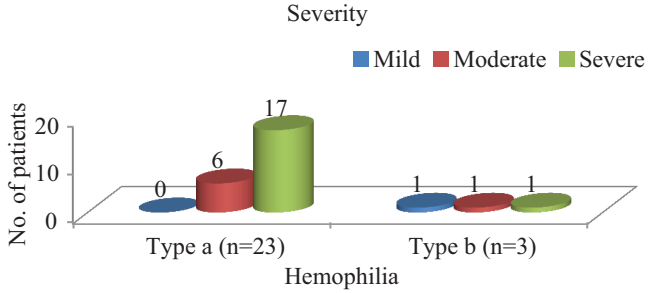

Figure-1: Type of hemophilia and grading of severity of hemophilia in group I patients

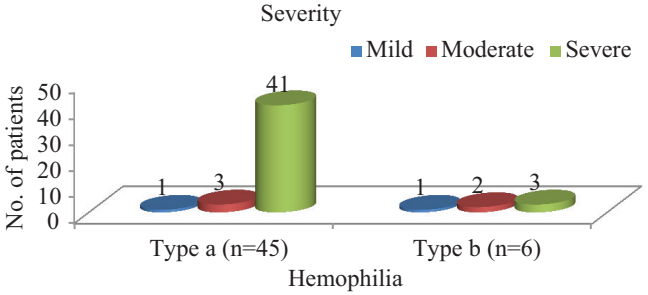

Figure-2: Type of hemophilia and grading of severity of hemophilia in group II patients

and out of these only knee joint involvement is found in 34.61% patients [Table 1].

In group II there were 51 patients. Out of these (n=51) 88.23% patients were found to be suffering from hemophilia A and 11.7% patients had hemophilia B. The ratio of hemophilia A to B is 7.5:1. Various target joints involvement is found in 88.23% patients. Out of these knee joint is the most commonly involved joint, and is found in 68.62% patients [Table 2].

In group I (n=26) family history of hemophilia is present in 69.23% patients and is absent in 30.76% patients. Significant association is found between family history and type of hemophilia in pediatric age group patients (*P*=0.005) [Table 3]. But no significant association is found between family history and age of diagnosis of hemophilia in group I patients (*P*=0.92). Family history did not influence the age of diagnosis and majority of the cases were diagnosed by the age of five years.

In group II (n=51) family history of hemophilia is present in 49.02% patients and is absent in about 50.98% patients. No significant association is found between family history and type of hemophilia in group II patients (*P*=0.41) [Table 4]. Also no significant association was found between family history and age of diagnosis of hemophilia in group II patients (*P*=0.84).

In group I (n=26), 69.23%, 26.92% and 3.84% patients respectively had severe, moderate and mild hemophilia [Fig.1]. In group II (n=51), 86.27% patients had severe, 9.80% patients had moderate, and 3.92% patients had mild hemophilia [Fig.2]. Among the total hemophilia patients (n=77), n=7(9.09%) patients were reactive for Hepatitis-C, n=5(7.35%) patients were reactive for Hepatitis-B and none for HIV 1 and 2 [Table 5].

DISCUSSION

Our study reported that hemophilia A is more common than hemophilia B. Our study included 77 patients of hemophilia with 93.3% having factor VIII deficiency and 6.7% having factor IX deficiency. The ratio of hemophilia A to B is 7.6:1 in group I and is 7.5:1 in group II. In our study majority of the hemophilia patients had severe deficiency of either factor VIII or factor IX. This may be due to under diagnosis of moderate and mild cases, and because mostly severe cases presents or referred for treatment at medical college/tertiary care centre. According to a study of descriptive epidemiology of hemophilia from Maharashtra (1989-2000), done on 1467 hemophilia patients showed that the ratio of hemophilia A:B was 4.2:1 with majority (85%) of patients were suffering from severe hemophilia A at the time of presentation.[11] Similarly a retrospective analysis done on 168 patients with hereditary bleeding disorders in Saudi Arabia, demonstrated

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hemophilia A predominance.[12] Also a study from Poland on 2269 hemophilia patients reported that majority of hemophilia A (59.7%) and B (56.8%) patients had severe hemophilia.[13]

Though hemophilia is an inherited disorder, it also has high rate of spontaneous mutation. Historically, around one in three cases of hemophilia have no family history. In our study 55.84% patients had a family history of hemophilia. Similarly a study from Poland on hemophilia patients reported that about 50% patients with hemophilia had no family history of hemophilia.[13] A study from United States which included 804 patients with hemophilia A or B reported positive family history of hemophilia in 70% of hemophilia patients.[14]

In our study 15.58% patients had delay of up to 5 years or more in the diagnosis from the first bleeding episode and 45.45% patients had delay up to 5 years or more in between diagnosis and specific factor replacement therapy. Similarly in a study from Maharashtra on patients with hemophilia, 27% patients were diagnosed with a delay of five years or more after the first bleeding episode.[11] The delay in diagnosis is probably due to poor awareness and inadequate diagnostic facility at most centers with limited resources of factor concentrate.

In group I various target joint involvement is found in 57.69% patients and knee joint involvement is found in 34.61% patients. This may reflect that this complication (hemarthrosis) is uncommon in young children and no patient developed permanent hemophilic joint disability. Similarly in a study on hemophilia children patients done in Egypt, showed that only 22.2% patients developed hemarthrosis and only 9.7% patients were on orthophysiotherapy and none of them had permanent joint disability.[15] In group II patients knee joint is the most common target joint (68.62%) and > 90% patients required orthophysiotherapy.

In our study a total of 77 hemophilia patients showed prevalence of 9.09% for Hepatitis-C, 6.49% for Hepatitis-B and nil for HIV-1 and 2. No case of co-infection of Hepatitis-C with Hepatitis-B or with HIV-1 and 2 was found in our study. In a study from Pakistan a total of 173 male patients with hemopihilia were screened and out of these, 89 patients were reactive for Hepatitis-C (51.4%). Only 3 out of 173 patients were reactive for Hepatitis-B and none for HIV.[16] Similarly a study from Zahedan, Southeast Iran, on patients with hemophilia showed seroprevalence of HCV in 29.6% and HBsAg in 4.9% patients.[17]

CONCLUSION

The conclusions of the present study are as follows: Hemophilia A is the most common type of hemophilia disorder present in the patients at tertiary care center of west UP. Majority of the reported cases have severe type of hemophilia at the time of presentation and majority of the cases were diagnosed by the age of 5 years. Most common presenting symptom at the time of diagnosis was soft tissue bleeding and knee joint is the most commonly involved joint. Hepatitis-C infection was more frequently identified than Hepatitis-B and HIV infections in patients with haemophilia with history of factor/blood transfusion.

Current study suggests that we need to formulate strategies to improve early diagnosis and treatment of hemophilia and implementation of blood donation system with standard screening methods, availability of viral inactivated factor concentrates, continuous awareness and enhanced safety measures.

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