Original Article

Clinicopathological features of hemophilia in a tertiary care centre of India

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Abstract

Context: Inherited bleeding disorders are common in India and hemophila and von Willebrand diseases are the most common among them. These patients can present in any department including paediatrics, medicine, orthopaedics and even gynaecology so knowledge about hemophilias and facilities for specialized tests for diagnosis are required. Few centres of north-eastern part of India perform these tests so hemophilias remain an underdiagnosed and underreported disease. **Aims:** The objective of this study was to estimate the prevalence of hemophilia in patients referred to this tertiary care centre and study the clinicopathological profile of these patients. **Settings and Design:** Prospective study. **Methods and Material:** Patients referred with suspicion of bleeding disorders in a time period of 4 years were evaluated. Complete clinical details, family history was retrieved and tests like complete blood counts, bleeding time, prothrombin time, activated partial thromboplastin time and factor assays were performed. **Results:** A total of 1126 patients with suspected bleeding disorder were tested and 237 were diagnosed of inherited bleeding disorders. Hemophilia A (HA) was diagnosed in 151 patients (63.7%), Hemophilia B (HB) in 31 (13%). Mean age was 10 years in HA and 11 years in HB patients. Clinical features of hemophilia varied according to Factor VIII levels. Coagulation type of bleeding such as hemarthrosis and hematoma were much more frequent than mucosal type bleeding. **Conclusions:** The present study is one of the very few studies from the north-eastern part of India estimating the prevalence and clinicopathological features of hemophilia, highlighting the need of specialized diagnostic facilities in this part of India.

Keywords: Hemophilia A, hemophilia B, inherited

Introduction

Factors VIII and IX deficiency are the commonest inherited bleeding disorders worldwide and patients can present in any department with bleeding manifestations. So, information about prevalence, clinical features, and investigations is essential for diagnosis and management of hemophilia. The diagnosis requires specialized tests performed in coagulation laboratories, which is one of the limiting factors as very few of the laboratories in the north east India are equipped to perform these specialized tests. The objective of this study was to bridge this gap of information by estimating the prevalence of hemophilia in patients referred to this tertiary care centre and study the clinicopathological profile of these patients.

Factor VIII (hemophilia A), Factor IX (hemophilia B), and von Willebrand's factor deficiency are the most common inherited coagulation defects. Both hemophilia A (HA) and hemophilia B (HB) show X-linked recessive inheritance. Factor XI deficiency also called hemophilia C is rarer, milder, and autosomally inherited.[1] HA and HB are classified in mild (5--40%), moderate (1--5%), and severe (<1% of normal) depending on factor levels.

Subjects and Methods

It is a prospective study conducted from time period of January 2014 to December 2018. Inclusion criteria include all patients

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referred to pathology department with suspected bleeding disorder. Clinical details were retrieved including age of onset, bleeding manifestations, family history, medication history, menstrual history in females, blood loss during dental/surgical procedures, and during neonatal period. 3.2% of sodium citrate was used as anticoagulant for coagulation and platelet studies, in 1: 9 ratio and processed within 4 hours. Ethylenediaminetetraacetic acid (EDTA) blood samples were used for complete blood counts, platelet count, and general blood picture. Platelet studies were done on platelet rich plasma and coagulation studies were done on platelet poor plasma. Laboratory analysis was done including prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time, correction experiment with normal plasma, normal aged serum and Al (OH) 3 adsorbed plasma. BT was done by modified Ivy's method. Specific factor assay for factors VIII and IX and vWF Antigen levels (vWF: Ag) was performed by Enzyme-linked immunoassay (ELISA) (Diagnostica Stago, France).

Results

A total of 1126 patients with suspected bleeding disorder were referred to our coagulation laboratory and evaluated in a time period of 4 years. Out of these 237 were diagnosed of inherited bleeding disorders. HA was most common inherited bleeding disorder, diagnosed in 151 patients (63.7%), HB in 31 (13%) and vWD was diagnosed in 38 (16%) of these 237 cases. The distribution of these 237 cases is tabulated in Table 1. In hemophilia A patients, age range was 1 month to 48 years, and mean age was 10 years. In hemophilia B patients, age range was 1 month to 36 years, and mean age was 11 years. All patients of hemophila were males except two females presenting with severe hemophila B phenotype. Family history was positive in 80 of 151 hemophila A patients (53%) and 14 of 31 hemophila B patients (45%). One out of the two females with hemophila B gave a positive family history. 11 patients of hemophila A and 2 patients of hemophila B gave history of consanguinity. History of blood transfusions was present in 75 (49%) patients of HA and 19 (61%) patients of HB. hemophila A and B can be classified in mild, moderate, and severe categories according to factor VIII levels <1% as severe, 1–5% as moderate and >5% as mild (normal 50–150%). Most diagnosed cases of HA (be 68%) and HB (84%) were in severe category [Table 2]. Clinical features of hemophilia varied according to Factor VIII levels [Table 3]. Clinical presentation of prolonged bleeding after trauma was present in all cases of severe HA and HB. 15% of mild HA patients and 36% of moderate HA patients had prolonged bleeding. Mild HB patients did not have prolonged bleeding and moderate showed prolonged bleeding in 50% of patients. Coagulation type of bleeding such as hemarthrosis and hematoma was much more frequent in HA and HB than mucosal type bleeding. Hemarthrosis was seen in 74% of severe HA and 88% of severe HB. Hematoma was seen in 90% of severe HA and 96% of severe HB. Whereas epistaxis was seen in just 12% of severe HA and 23% of severe HB, petechiae, purpura was seen in 4% of severe HA and 8% of severe HB. Hematemesis and/or malena in 12% of severe HA and 15% of severe HB. Haematuria in 9% of severe HA and 8% of severe HB and gum bleeding in 26% of severe HA and 23% of severe HB.

Table 1: Distribution of inherited bleeding disorders

	n	%
Hemophilia A	151	63.7
Hemophilia-B	31	13.1
von Willebrand Disease	38	16.0
Platelet Disorder	10	4.2
Factor-XIII	5	2.1
Factor-X	1	0.4
Factor-VII	1	0.4
Total	237	100.0

Table 2: Disease severity of patients with hemophilia

Total number	Hemophilia A (*n*=151)	Hemophilia B (*n*=31)
Age (mean)	10 years	11 years
Mild deficiency (5-50%)	20 (13%)	3 (10%)
Moderate deficiency (1-5%)	28 (19%)	2 (6%)
Severe deficiency (<1%)	103 (68%)	26 (84%)

In laboratory evaluation of inherited bleeding disorders, the first line of investigations includes complete blood counts with platelet count, blood picture, bleeding time, PT and APTT. In the present study, platelet count and bleeding time was normal in all patients. PT was normal in nearly all patients and APTT was raised and correlated with the severity and Factor VIII levels [Table 4]. Mean APTT was 50, 66, and 89 s in mild, moderate, and severe HA, respectively. Similarly, mean APTT was 50, 61, and 106 s in mild, moderate, and severe HB, respectively. Factor VIII and Factor IX levels were determined for confirmation of hemophilia. Mean Factor VIII levels were 9, 2.3, and 0.7% in mild, moderate, and severe HA, respectively. Mean Factor IX levels were 10.9, 1.7, and 0.6% in mild, moderate, and severe HB , respectively. von Willebrand factor levels were normal in all the patients.

Discussion

Hemophilias and von Willebrand disease are the commonest inherited bleeding disorders worldwide and in India. Hemophilia A (classical hemophilia) and B (Christmas disease) are the most common types of hemophilia with deficiency of Factors VIII and IX, respectively. Incidence of hemophilia A is approx. 1 in 10000 people and it is five times more common than hemophilia B.[2] HA and HB are X linked diseases and genes for HA is located in the tip of the long arm of X chromosomes in band Xq28 and for HB in band Xq27. Majority of severe HA have large deletions or inversions (intron 22, intron 1) leading to major defects of factor VIII. In HB there are no large deletions or inversions like HA, so some function is retained in the mutated protein also resulting in lesser severity of HB than HA. In about 30% of hemophilia patients, there is no family history and is caused due to spontaneous mutations.[2] In the present study family history

Table 3: Clinical features of patients with hemophilia

	Hemophila A			Hemophila B		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Age (mean)	9	10	18	10	11	11
Prolonged bleeding on trauma (%)	3 (15%)	10 (36%)	103 (100%)	0	1 (50%)	26 (100%)
Petechiae/purpura (%)	2 (10%)	1 (3.5%)	4 (4%)	0	0	2 (8%)
Hematemesis/malena (%)	4 (20%)	3 (11%)	12 (12%)	0	0	4 (15%)
Haematuria (%)	2 (10%)	1 (3.5%)	9 (9%)	0	0	2 (8%)
Epistaxis (%)	4 (20%)	5 (18%)	12 (12%)	1 (33%)	0	6 (23%)
Hemarthrosis (%)	6 (30%)	16 (57%)	74 (74%)	1 (33%)	1 (50%)	23 (88%)
Hematoma (%)	15 (15%)	16 (57%)	90 (90%)	2 (67%)	2 (100%)	25 (96%)
Gum bleeding (%)	7 (35%)	6 (21%)	26 (26%)	0	0	6 (23%)

Table 4: Laboratory features of patients with Hemophilia

	Hemophilia A			Hemophilia B		
	Mild	Moderate	Severe	Mild	Moderate	Severe
PT control (mean)	13-13.5 (13.3) s	13-13.5 (13.3) s	13-13.5 (13.3) s	13-13.5 (13.3) s	13-13.3 (13.2) s	13-13.5 (13.3) s
PT test (mean)	13-15.5 (13.5) s	12.9-16 (13.9) s	12.7-16.5 (13.9) s	13.5-13.6 s	12.4-13.7 (13) s	13-17 (13.7) s
APTT control (mean)	27-30 (28) s	27-30 (28) s	27-30 (28) s	28-29 (28.5) s	28-29 (28.5) s	27-30 (28) s
APTT test (mean)	40-62.3 (50) s	46.5-103 (66) s	66.9-120 (89) s	43-56 (50) s	60-62 (61) s	68-135 (106) s
FVIII	5.4-16 (9)	1-5 (2.3)	0.3-0.99 (0.7)	Normal	Normal	Normal
FVIII control	84-120 (104)	84-130 (108)	84-130 (110)	Normal	Normal	Normal
FIX	Normal	Normal	Normal	6-15.8 (10.9)	1.2-2.1 (1.7)	0.3-0.96 (0.6)
FIX control	Normal	Normal	Normal	108-114 (111)	84-120 (102)	89-130 (104)
Platelets	Adequate	Adequate	Adequate	adequate	Adequate	Adequate

was present in 53% of HA and 45% of HB patients. Remaining could have been due to spontaneous mutations or transferred by mildly affected or carrier parents who were asymptomatic and undiagnosed. Study by Sahoo *et al.* also showed positive family history in nearly half of the cases.[3]

In the present study, the age of presentation was earlier in severe HA than mild or moderate HA patients, and severe HA may present as early as child beginning to crawl or walk. Hemarthrosis in weight bearing joints is typical manifestation of HA and leads to deformity in long term. All the affected patients of HA are males and only two of all HB patients are females in this study. Females are mostly carriers but in some special cases they can be affected due to lyonisation of normal x chromosome very early in embryogenesis, or in case of female offspring of affected male and carrier female.[2] Several other studies have also highlighted issue of bleeding in women with hemophilia. They should be investigated for factor deficiency and other bleeding disorders and management according to severity should be done.[4]

The distribution of mild, moderate, and severe cases in HA in present study was 13%, 19%, and 68%, whereas in HB was 10%, 6%, and 84%, respectively, which indicates a much higher prevalence of severe hemophilia. Other studies from India showed similarly high percentages of severe hemophilia [Table 5].[3,5-8] Study by Kumar *et al.* from the same centre as the present study showed 63% of severe HA and 62% of severe HB.[5] A study by John *et al.* showed 63% of hemophilia patients had severe hemophila .[6] Although data from the high-income countries showed prevalence of 39%, 14%, and 45% of mild, moderate, and severe cases, respectively.[9] The relatively increased proportion of cases of severe hemophilia in present study and other Indian studies could be due to referral bias of patients with severe hemophilia compared to mild and moderate hemophilia. Nearly, all the studies from India are done on patients referred to hospitals and cannot accurately determine the prevalence of mild disease in general population; consequently, hemophilia is an underdiagnosed and undertreated disease in our healthcare system.

Hemophilia patients can present with diverse clinical manifestations and may require lifelong management. The first point of contact and care remains primary care physicians, and the diagnosis and management of mild to moderate symptoms can be undertaken on a home based or day-care centre by primary care physician. This study will supplement the information on prevalence, clinical features, and laboratory diagnosis of hemophilia so the physicians will be able to diagnose and manage the patients of inherited bleeding disorder especially hemophilia. Diagnosis is mandatory for starting management of the patients. The role of primary care physician is to provide routine prophylaxis which may also include administration of clotting factors to reduce morbidities like joint deformity.[10] Prompt initiation of factor replacement therapy in case of bleeding will help prevent loss of precious time before reaching specialized centres for therapy initiation. Also, it will reduce the load of specialized centres especially in India where population is huge and tertiary care centres are few. A lot more is needed to

Table 5: Comparison of Indian studies on hemophila

	HA	HB	Mean age (years)	Gender (M: F)	Severe hemophila	Hemarthrosis	Transfusion transmitted infections	Inhibitors	Positive family history
John *et al.*[6] (*n*=211)	175 (91%)	36	22	_	132 (62.5%)	37 (31%)	24 (18.3%)	7.9%	93 (52%)
Kumar *et al.*[5] (*n*=92)	79 (86%)	13 (14%)	14	All M	63% (HA), 62% (HB)	38 (41%)		3.5%	
Sajid *et al.*[7] (*n*=408)	212 (51.9%)	24 (5.8%)	17	4:1	46 (21.6%)	48%	9 (2.2%)		196 (48%)
Sahoo *et al.*[3] (*n*=426)	308 (72.3%)	49 (12%)	3	1 F, all others M	65% (HA), 87% (HB)	34%	-	1 case	55% (HA) 47% (HB)
Ahmed *et al.*[8] (*n*=1576)	52%	8%	-	-	78% (HA), 70% (HB)	-	-	-	-
Present study (*n*=237)	64%	13%	10	2 F, all others M	68% (HA), 84% (HB)	74% (HA), 88% (HB)	-	-	53% (HA) 45% (HB)

be done for prevention and treatment of hemophilia and related diseases such as transfusion transmitted infections, especially in the rural population of the country. The present study is one of the fewer studies from north-eastern part of India studying the demographic and clinicopathological features of hemophilia. As very few centres provide the tests required for diagnosis of inherited bleeding disorders, data from this part of the world is very limited.

The differential diagnosis of reduced Factor VIII levels includes primarily von Willebrand disease which can be excluded by evaluation of VWF levels and functional assays, which were normal in the patients diagnosed as hemophilia in the present study. Ratio of VIIIc: VWF is low in HA and variable in von Willebrand disease.[2] Combined factor V and VIII deficiency and disseminated intravascular coagulation will show elevated PT and APTT.

Conclusion

This study is one of the few studies from the north-eastern part of India estimating the prevalence and clinicopathological features of hemophilia. Among all the inherited bleeding disorders, hemophilia A is the commonest, and in hemophilia patients, severe form is the commonest, although there may be some referral bias. Hemophilia requires specialized tests for diagnosis and life-long support which is a limitation for the vast rural population in north-east part of India. The role of primary care physicians is extremely important in providing routine care, emergency treatment of bleeding, follow-up and check for anaemia due to haemorrhage, transfusion transmitted infections and joint deformity. Also, by prophylactic administration of clotting factors in severe hemophilia, physicians can reduce morbidity and mortality related to severe hemophilia. Although the future looks promising with the recent advances in therapy including gene therapy, there is a huge unmet need of diagnostic and treatment facilities in this part of India.

Ethics

This study is approved by the institutional ethics committee on 21/05/2015

Key Messages:

Underdiagnosis of inherited bleeding disorders due to lack of specialized coagulation laboratories a limitation in care of patients with hemophilia, especially when there is a definite advantage of routine care and prophylaxis in severe cases.

Literature on women with hemophilia is scarce but the present study shows women should also be investigated for hemophilia.

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Conflicts of interest

There are no conflicts of interest.

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