Clinical profile of hemophilia B patients from Karnataka

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Abstract

Background: The most prevalent severe inherited hemorrhagic condition is hemophilia, which means "love of blood." Hemophilia A and B are caused by a lack or malfunction of the factor VIII and factor IX proteins. **Objective:** The present study is to determine the prevalence and clinical profile of hereditary coagulation disorder, particularly hemophilia B, in Karnataka. **Methods:** The study comprised 150 HB patients with a mean age of 25, n_{male} = 148 and n_{female} = 2. The samples were collected from hemophilia societies across Karnataka. The detailed history of HB patients was recorded in a predesigned Performa regarding family history, age, time of first bleed, site of the bleed, and bleeding history. **Result:** In our study cohort, the majority of the 58 (38.7%) cases belong to 21–30 years of age. The mean age of onset was 2.0 ± 1.0 years in severe, $7.5 \pm 2.8\,0$ years in moderate, and 10.0 ± 3.5 years in mild HB patients. Out of 150 HB cases, 102 (68%) cases were diagnosed as severe, 30 (20%) as moderate, and 18 (12%) as mild. Mean factor IX levels were 0.6 ± 0.2, 2.5 ± 1.3, and 8.0 ± 2.6 in the severe, moderate, and mild group, respectively. A family history of bleeding was observed in 97 [64.7%] HB patients. Forty-seven (32.3%) HB patients had a history of consanguinity. The most common initial site of bleed was in joints in 86 [57.3%]. **Conclusion:** The present study is one of the fewer studies from Karnataka studying the demographic and clinicopathological features of hemophilia B. Early diagnosis can be only helpful with knowledge of spectral presentation of hemophilia B in a local population.

Keywords: Epidemiology, F9 gene, hemophilia B, Karnataka

Introduction

Bleeding disorders like hemophilia A [classic hemophilia] and hemophilia B [Christmas disease] are the most common inherited disorders worldwide and India. The World Federation of Hemophilia estimates that there are 4,00,000 individuals worldwide with hemophilia; among them, 80% are in India.[1] HA and HB are X-linked diseases and genes which are responsible for HA located in the long arm of the X chromosome [Xq28] and HB located in the long arm of the X chromosome [Xq27].[2,3]

The two most common forms of hemophilia are hemophilia A [HA] and hemophilia B [HB]. HA comprises approximately 80% of total hemophilia cases, and HB comprises 20% of hemophilia cases.[4] Approximately 30% of the patients have no family history and are results of de novo mutations. HA occurs in 1 out of 10,000 male births, while HB occurs in 1 out of

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25,000 male births.[5,6] One of the most frequent coagulation abnormalities is factor deficiency (factor VIII and factor IX). Both hemophilia A and hemophilia B are inherited in a recessive X-linked manner.[2]

The clinical hallmark of hemophilia is bleeding into soft tissues, muscles, and joints. In developing and crowded nations like India, where patients with hemophilia have limited access to the treatment further, repeated use of blood and blood products as a cheaper alternative to factor concentration increases the risk of transfusion transmitted infections.[1,7]

The present study aims to determine the prevalence and clinical profile of hereditary coagulation disorder, particularly hemophilia B, in Karnataka. To learn more about the prevalence and clinical characteristics of hemophilia, it is necessary to diagnose the disease and manage it. The goal of this research was to learn more about the clinicopathological characteristics of hemophilia patients.

Materials and Methods

A cross-sectional study was conducted during 2018–2020. Ethical approval for the study was obtained from Shri B. M. Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapura (Ref No.: BLDE (DU)/IEC/340/2018-19) and SNMC institutional ethics committee of human subjects research, Bagalkot (SNMC/IECHSR/2018-19/A-B2/1.1). Totally, 150 HB patients [mean age = 25; n_{male} = 148 and n_{female} = 2] were included in the study. The samples were collected from hemophilia societies across the Karnataka State of India. The detailed history of HB patients was recorded in a predesigned Performa regarding family history, age, time of first bleed, site of the bleed, and bleeding history. Factor assay was carried out by using a "one-stage assay" using a semi-automated clot analyzer. Factor level <1% [<0.01 IU/mL], 1–5% [0.01–0.05 IU/mL], and >5%–<40% [>0.05–<0.4 IU/mL] was defined as severe, moderate, and mild, respectively.[8] The obtained data were tabulated and analyzed via SPSS 15.0 (SPSS Inc., Chicago, USA). Data are presented as mean ± SD.

Student's t test and one-way ANOVA were used to compare the significant difference in mean. For categorical variables, the Chi-square test was used. *P* value < 0.05 is considered statistically significant.

Results

One hundred and fifty patients suffering from hemophilia B were included in the present study. Our study cohort includes 148 male and 2 female HB patients. The age of the patients ranges from 5 to 35 years, and the mean age was 25 years. In our study cohort, the majority of the 58 (38.7%) cases belong to 21–30 years of age followed by 11–20 years (41) (27.3%). The mean age of onset of symptoms was 2.0 ± 1.0 years in severe patients, 7.5 ± 2.8 years in moderate patients, and 10.0 ± 3.5 years in mild HB patients [Table 1].

Table 1: Age distribution of patients (*n*=150)		
Age-group	No.	Percentage
1-10	18	12%
11-20	41	27.3%
21-30	58	38.7%
31-40	33	22%

Out of 150 HB cases, 102 (68%) cases were diagnosed as severe, 30 (20%) cases were diagnosed as moderate, and 18 (12%) cases were diagnosed as mild. 2 female HB patients were diagnosed as severe. Mean factor IX level was 0.6 ± 0.2, 2.5 ± 1.3, and 8.0 ± 2.6 in the severe, moderate, and mild group, respectively.

In our study, family history of bleeding was observed in 97 [64.7%] HB patients. Among those, 80 [82.5%] cases belong to the severe group, 10 [10.3%] belong to the moderate group, and 7 [7.2%] belong to the mild group, respectively. Forty-seven (32.3%) HB patients had a history of consanguinity.

The most common initial site of bleed was in joints in 86 [57.3%] HB patients followed by skin in 27 [18%], muscle in 16 [10.7%], epistaxis in 11 [7.3%], and petechiae in 10 [6.7%] hemophilia B patients, respectively. The present study shows 38 (25.3%) HB patients were inhibitor positive. The detailed clinicopathological characteristics are given in Table 2.

Discussion

Bleeding disorders like hemophilia A [classic hemophilia] and hemophilia B [Christmas disease] are the most common inherited disorders worldwide and India. HA is more common than HB. Being an inherited disorder, family history has been observed in 45–47% of cases of hemophilia B patients.[2,9] In our study, 97 [64.7%] HB patients have a family history of bleeding disorder. Remaining may be due to spontaneous mutations or transferred by mildly affected or carrier parents who were asymptomatic and undiagnosed.[9]

The majority of the cases (96%) have bleeding manifestation before 5 years of age[10] with the mean age of onset ranging from 9 to 11 months depending upon severity.[11] In our study, the mean age of onset of symptoms was 2.0 ± 1.0 years in severe patients, 7.5 ± 2.8 0 years in moderate patients, and 10.0 ± 3.5 years in mild HB patients. Karim MA *et al.* 2013 reported that the mean age onset was 15.8 years.[10] All the patients in the present study were male except two females. Hemophilia A and hemophilia B are X-linked disorders; it most commonly affects the male. Females act as a carrier.

In the present study, 102 (68%) HB patients having <1% of factor IX concentration designated as severe, 30 (20%) cases having 1–5% of factor IX concentration designated as moderate, and 18 (12%) cases having >5–<40% of factor IX concentration designated as mild. In the study, Ahmad *et al.*[12] 2008 reported that 69.6% of hemophilia B patients had a severe,

Clinicopathological parameters	Severity of disease			P
	Severe (Factor IX <1%) *n*=102 (68%)	Moderate (Factor IX 1-5%) *n*=30 (20%)	Mild (Factor IX >5%) *n*=18 (12%)	
Mean factor IX levels (%)	0.6±0.2	2.5±1.3	8.0±2.6	0.001*
Family history of bleeding (*n*)	80	10	7	
Mean age of onset (years)	2.0±1.0	7.5±2.8	10.0±3.5	0.001*
Inhibitor positive (*n*)	23	11	04	
Inhibitor negative (*n*)	79	19	14	
Bleeding sites				
Joints	55 (54%)	19 (63.3%)	12 (66.7%)	
Skin	17 (16.7%)	6 (20%)	4 (22.2%)	
Muscle	13 (12.7%)	1 (3.3%)	2 (11.1%)	
Epistaxis	7 (6.9%)	4 (13.3%)	0	
Petechiae	10 (9.8%)	0	0	

Table 2: Clinicopathological characteristics of hemophilia B patients of our study cohort

19.2% had a moderate, and 11.2% had a mild condition. The study by Sahoo *et al.*[9] 2020 and Pawan *et al.*[2] 2021 showed a higher percentage of severe hemophilia cases, i.e., 87% and 84%, respectively.

The initial bleeding site depends upon level factors. In a place where circumcision is a routine practice, post-circulation bleed is the most common initial bleed [51%–62%].[1] Joint bleed [hemarthrosis] is the most common [82%–100%]. Ahmad *et al.*[12] reported the most common presenting features in hemophilia as hemarthrosis in 82%. Hemarthrosis is most common in 72.85% of HB cases followed by skin bleed [77–90%].[10,13-15] In the present study, joint bleeds [hemarthrosis] were the most common clinical manifestation (57.3%), followed by skin bleed in 18%, muscle in 10.7%, epistaxis in 7.3%, and petechiae in 6.7%. The study by Pawan *et al.* 2021 shows 88% of hemarthrosis and 96% of hematoma in severe HB patients, but our study recorded a low rate of hemarthrosis [54%] and hematoma [16.7%] in severe HB.[2] This may be due to differences in the geographical region and population. In our study, family history of bleeding was observed in 97 [64.7%] HB patients and it is high compared to the study conducted by Pawan *et al.*[2] 2021, and Sahoo *et al.*,[9] 2020 showed positive family history in 45% and 47%, respectively.

Patients with hemophilia B might have a wide range of clinical symptoms and require proper management for the rest of their life. Primary care physicians are the first point of contact for diagnosis and treatment. Our study provides knowledge about hemophilia B prevalence, clinical features, and laboratory diagnosis; this will help the physicians for better diagnosis and early treatment. Only a few clinics offer the testing such as factor concentration and mutation analysis needed to diagnose inherited bleeding problems in our population. Several previous studies from India carried out on hemophilia B were referred to hospitals, and those were not properly determining the severity of the disease in our population. So the present study provides better understanding of concentration of factor levels with respect to severity of the hemophilia B, and it also provides demographic and clinicopathological aspects of hemophilia B in the present study population.

Conclusion

Hemophilia is common worldwide; it shows heterogeneous presentation upon the disease severity over different populations. The present study is one of the fewer studies from the Karnataka region of India studying the demographic and clinicopathological features of hemophilia B. In India, hemophilia inhibitor screening and other genetic tests are not commonly available for the identification and management of the patient. Care of hemophilia is complex, often requiring health management beyond the prevention and treatment of bleeding. Early diagnosis can be only helpful with knowledge of spectra presentation of hemophilia B in a local population.

Key points

Proper detailed early diagnosis of hemophilia B with respect to factor level, family history, severity of the disease, and clinical features is required for the proper treatment and future management.

The present study provides much needed information for physicians and clinicians of care centers for proper early diagnosis and management of the disease.

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Conflicts of interest

There are no conflicts of interest.

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