Original Article

Clinical profile of hemophilia patients in Jodhpur Region

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Abstract:

Background: Hemophilia is widely distributed all over the world, but little is known about its clinical profile in resource-limited regions. An insight into its clinical spectrum will help in the formulation of policies to improve the situation in these areas. **Aims:** To study the clinical profile of hemophiliacs (age <18 years) in Jodhpur region and screen them for transfusion-transmitted infections. **Materials and Methods:** A cross-sectional study conducted in the Department of Pediatrics, Umaid Hospital, Dr. S. N. Medical College, Jodhpur, over a period of 12 months. **Result:** Out of a total of 56 cases enrolled, 51 (91%) cases were diagnosed as hemophilia A while 5 (9%) were diagnosed as hemophilia B. Positive family history was found in 26 (46%) cases. According to their factor levels, 25 (44%) cases had severe disease, 20 (36%) had moderate disease, and 11 (20%) had mild disease. The mean age of onset of symptoms and diagnosis was 1.73 ± 1.43 and 3.87 ± 3.84 years, respectively. First clinical presentation was posttraumatic bleed in 20 (36%), gum bleeds in 17 (30%), epistaxis in 4 (7%), joint bleeds in 4 (7%), skin bleeds in 4 (7%), and circumcision bleed in 3 (5%) cases. Knee joint was the predominant joint affected by hemarthrosis in 38 (68%), followed by ankle in 29 (52%), elbow in 20 (36%), and hip joint in 7 (13%) cases. All patients had a negative screening test for transfusion-transmitted infections. **Conclusion:** Occurrence of posttraumatic bleeds and gum bleeds in an otherwise normal child should warn the clinician for evaluation of hemophilia.

Key words:

Clinical manifestation, hemarthrosis, hemophilia

Introduction

Hemophilia is an X-linked heritable coagulopathy with an overall prevalence of approximately 1 in 10,000 individuals. The two most common forms are factor VIII deficiency or hemophilia A, which comprises approximately 80% of cases and factor IX deficiency or hemophilia B, which comprises approximately 20% of cases.[1,2] The incidence of hemophilia A (classical) is 1/5000 male births, and that of hemophilia B (Christmas disease) is 1 in 25,000.[3] Approximately, 30% of the patients have no family history and are a result of de novo mutations.

The clinical hallmark of hemophilia is bleeding into soft tissues, muscles, and joints. Factor levels of <1% (<0.01 IU/mL), 1-5% (0.01-0.05 IU/mL), and >5-<40% (>0.05-<0.40 IU/mL) define the severe, moderate, and mild phenotype (normal values = 50-150%), respectively.[4] Patients with the mild and moderate disease generally bleed after significant trauma or major surgery; those with the severe form may bleed spontaneously or after minor trauma.

In developing nations such as India, where patients with hemophilia have limited access to treatment, there is widespread disability from recurrent joint bleeds, and morbidity from joint impairment increases significantly with advancing age.[5] Furthermore, repeated use of blood and blood products as a cheaper alternative to factor concentrate increases the risk of transfusion-transmitted infections.

The World Federation of Hemophilia estimates that there are 4,00,000 individuals worldwide with hemophilia.[6] Out of them, 80% are in developing countries such as India.[7] In most of the developing countries, a very small amount of resources is spent on diseases such as hemophilia. Under such circumstances, data collection for hemophilia acquires very low priority. The paucity of data in the developing world makes it very difficult to accurately represent the situation regarding the epidemiology, clinical profile, diagnosis, and treatment of hemophilia. This study was designed

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for assessment of the clinical profile of hemophilia patients in our local population.

Materials and Methods

It was a cross-sectional study conducted in the Department of Pediatrics, Umaid Hospital, Dr. S. N. Medical College, Jodhpur, over a period of 12 months. A total of 56 diagnosed cases of hemophilia (diagnosed by factor assay) aged <18 years and resident of Jodhpur region were included in the study. A call for hemophilic patients of this region to come to the hospital and get registered was made through newspaper advertisements, pamphlets, and notices placed in the hospital campus. All patients known or suspected to be hemophiliacs were asked to get themselves enrolled in the hemophilia registry created under the "Mukhya Mantri BPL Jeevan Raksha Kosh Yojana" of the Government of Rajasthan.

A detailed history was recorded in a predesigned proforma regarding family history, age of first bleed, site of first bleed, age of diagnosis, bleeding history of last 1-year, age of first joint bleed, most affected joints in decreasing order of frequency, treatment type, and treatment products used. All new cases were subjected to factors VIII and IX assay (also if not previously done). In old cases, factor level were reconfirmed only in cases where it had been done within 24 h of receiving factor VIII/IX or blood products or method employed was not one-stage assay. Factor assay was done by "one-stage assay" using semi-automated clot analyzer. This is based on a comparison of the ability of dilutions of standard and test plasmas to correct the activated partial thromboplastin time of plasma known to be totally deficient in FVIII but containing all other factors required for normal clotting. Factor level of <0.01 IU/mL (<1%), 0.01-0.05 IU/mL (1-5%), and >0.05-<0.40 IU/mL (>5-<40%) defined as severe, moderate, and mild hemophilia, respectively. All cases were also screened for hepatitis B, hepatitis C, and HIV.

In the statistical method, descriptive analysis of qualitative variables was expressed in frequency and percentages. Statistical average was done by mean value and dispersion measured by standard deviation.

Results

Out of a total of 56 cases, 51 (91.07%) cases were diagnosed as hemophilia A while five cases (8.92 %) were diagnosed as hemophilia B. The study group comprised only males indicating its X-linked recessive inheritance. Positive family history was found in 26 (46.42%) cases. According to their factor level, 25 (44%) cases had severe disease, 20 (36%) had moderate, and 11 (20%) had mild disease [Table 1].

In the study group, majority (42.85%) of cases belonged to 1-5 years age group, followed by 32% cases in 5-10 years age group, and the mean age of studied group was 6.8 ± 4.5 years. Three patients (5.35%) had their onset of symptoms prior to 1-month but none was diagnosed in that period. Similarly, by 5 years of age though majority (93%) had experienced symptoms but only 77% were diagnosed by that time. Mean age of onset of symptoms was 1.73 ± 1.43 years while mean age of diagnosis was 3.87 ± 3.84 years [Table 2].

Usual clinical manifestations were different from those of first. The most common initial site of bleed was posttraumatic in 20 (35.7%), followed by gum bleed in 17 (30.35%) patients whereas ecchymoses and hemarthrosis were the usual manifestations in majority (80.35% and 73%), respectively [Table 3].

Knee joint (67.85%) was predominantly affected by hemarthrosis followed by ankle (51.78%), elbow (35.71%), hip (12.5%), shoulder (5.35%), and proximal metacarpophalangeal (1.78%) joint [Table 4].

Twenty-six patients (46.42%) had 1-5 bleeding episodes in the last 1-year. Eight (14.28%) cases had >10 bleeds in the last year. The mean annual number of bleeds was 6.5 ± 9/year. Thirty patients (53.57%) developed 1-5 joint bleeds in the last 1-year. More than 10 bleeds were present in 4 (7.14%) cases. The mean number of joint bleeds was 3 ± 5/year.

Table 1: Hemophilic cases according to their severity

Factor levels	Total *n* (%)
<1% or <0.01 IU/ml (severe)	25 (44.64)
1-5% or 0.01-0.05 IU/ml (moderate)	20 (35.71)
>5-40% or >0.05-0.4 IU/ml (mild)	11 (19.64)

Table 2: Age of onset and diagnosis of hemophilia

Age group	Total *n* (%)	Age of onset of symptoms *n* (%)	Age of diagnosis *n* (%)
<1-year	3 (5.35)	29 (51.78)	14 (25)
1-5 years	24 (42.85)	23 (41.07)	29 (51.78)
5-10 years	18 (32.14)	4 (7.14)	9 (16.07)
10-15 years	7 (12.50)	—	2 (3.57)
>15 years	4 (7.14)	—	2 (3.57)

Table 3: Clinical manifestation of hemophilia

Clinical feature	Usual presentation *n* (%)	First manifestation *n* (%)
Skin bleeds	45 (80.35)	4 (7.14)
Joint bleeds	41 (73.21)	4 (7.14)
Muscle bleeds	26 (46.42)	—
Bleeding gums	28 (50)	17 (30.35)
Epistaxis	15 (26.78)	4 (7.14)
GI bleed	2 (3.57)	—
Hematuria	1 (1.78)	—
Iliopsoas muscle hematoma	1 (1.78)	—
Posttraumatic	—	20 (35.71)
Circumcision	—	3 (5.35)
Tooth extraction	—	1 (1.78)
Umbilical bleed	—	1 (1.78)
Cephalohematoma	—	1 (1.78)
Postsurgical	—	1 (1.78)

GI: Gastrointestinal

Table 4: Frequency and distribution of hemarthrosis in hemophilia

Joints involved	Total *n* (%)
Knee	38 (67.85)
Ankle	29 (51.78)
Elbow	20 (35.71)
Hip	7 (12.50)
Shoulder	3 (5.35)
MCP	1 (1.78)

MCP: Metacarpophalangeal

All patients had received episodic treatment. A maximum of 40 (71%) patients had received cryoprecipitate, 22 (39%) had fresh frozen plasma, and 25 (45%) had clotting factors. Whole blood was transfused in 24 (43%) cases. All patients had a negative screening test for transfusion-transmitted infections, that is HIV, hepatitis C virus (HCV), and hepatitis B surface antigen (HB_sAg).

Discussion

Hemophilia A is more common than hemophilia B. In most of the studies, hemophilia A constituted around 80% of total hemophilias.[8-12] In Pakistani population, proportion of hemophilia A was found to be low (65%),[13] in contrast in our study, it was slightly higher than previous studies (91% vs. 80%). Based on severity, hemophilia is further classified into mild, moderate, and severe, last one being the most prevalent with its proportion ranging from 43% to 55.7%.[12,14-16] In the present study also, severe was the most prevalent (44.64%), and mild was the least prevalent (19.64%). In a striking contrast in Bangladesh, mild variety was found to be the most prevalent.[8,9]

Variations in prevalence rates and disease severity could be due to geographic differences, racial differences, variations in case finding, variations in hemophilia awareness and public health services, and dissimilar diagnostic methodologies due to a lack of standardized laboratory testing.

Being an inherited disorder, family history has been observed in 40-71% cases of hemophilias.[9,10,13,16] In our study also, it was positive in 46.42% cases. Majority of pediatric patients (94%) has bleeding manifestations before 5 years of age[9] with mean age of onset ranging from 9 to 11 months depending upon the severity.[14] In our study also, 93% had their onset before 5 years of age with the mean age of onset of symptoms being 1.73 ± 1.43 years. Despite early age of onset (<5 years), only 65-73% are diagnosed till 5 years of age.[13,17] In the present study, this percentage was slightly higher (77%) with mean age of diagnosis being 3.87 ± 3.84 years.

Initial bleeding site depends upon local factors. At a place where circumcision is a routine practice, postcircumcision bleed has been found to be the most common initial bleed (51.4-62% of the case).[13,18] Barring this, posttraumatic bleed has been found to be the most common initial manifestation of hemophilias[13,18] as in our study also, it was observed in 36% of cases.

Joint bleed (hemarthrosis) has been found to be the most common (82-100%) presenting feature followed by skin bleeds (77-90%).[8,9,16,19] In the present study also, skin bleeds and hemarthrosis were the most common clinical manifestations but former (80%) was more common than the latter (73%). Our study was restricted to pediatric subjects only, and this may be the reason of slightly lower frequency of hemarthrosis. Among the joints affected, knee is the commonest (33-68%) followed by elbow and ankle joints.[9,20] In our study also, knee joint was predominant (68%) but ankle joint (52%) was more common than elbow joint (36%). Similarly, more involvement of ankle joint was reported in a study in Bangladesh.[13] Our results may be due to more involvement of knee joint with an abnormal gait, which predispose to repetitive ankle hemarthrosis or may be due to higher physical activity due to lack of public awareness for hemophilia in our setup.

While evaluating a case of bleeding neonate, a possibility of hemophilia should also be kept in mind despite the known fact that Vitamin K deficiency is far more common. Severe hemophilia may present with intracranial hemorrhage (ICH) as the only presenting feature in newborns in 1-4% cases[21-26] and this estimate may be further higher, as it is mostly based on retrospective studies of infants who survived until the diagnosis was made. High mortality and significant morbidity; at least one-third of the survivors developing long-term sequelae, enforces the need of uncovering hemophilia in neonatal ICH. In the present study, no patient had a history of ICH in the newborn period, probably had expired, if any.

As the adult level of factor VIII is achieved at birth both in term and preterm newborns, hemophilia can be unmasked during the neonatal period also. Unlike FVIII, FIX is Vitamin K-dependent, so levels are significantly reduced at birth and are further reduced in preterm infants.[27,28] While it is usually possible to make a diagnosis of severe or moderate hemophilia B, infants who may be mildly affected will require repeat screening at 3-6 months of age. In developed countries, 64-75% of severe hemophilia cases have been diagnosed in the neonatal period only[24,29,30] while in developing countries it is usually missed in this period. In our study also, 3 out of 56 patients had a history of bleeding manifestations in the neonatal period but none of them were subjected to testing for hemophilia during that time, further emphasizing the need of clinical awareness.

In Western studies, use of factor concentrates range from 74% to 100%.[12,14,30] In the present study, only 45% had received factors. In our study, low factor transfusion rates are attributed to the poor economic status of the patients who could not afford factor replacement therapy.

In 1996, certain steps were taken to minimize the risk of transfusion-related/transmitted infections. These include to quarantine plasma until the donor has been tested or even retested for antibodies to HIV, hepatitis C, and HBsAg. Similarly, clotting factors are now subjected to viral inactivation procedures (such as heat or solvent/detergent treatment). All these steps have resulted in reduced risk of transfusion-related/transmitted infections since 1996. Prior to that, seroprevalence of hepatitis B and hepatitis C among hemophiliacs correlates well with the duration of treatment with clotting factors; in Iran (2002) 26.7% and 71.3%, respectively, and in India (2008-09) 5% and 7.5%, respectively.[11,31-33] In the present study; screening tests for HCV, HBV, and HIV all were negative, possibly due to the selection of younger hemophiliacs (age <18 years), who had been treated with plasma products after 1996.

Conclusion

Hemophilias are distributed worldwide and have heterogeneous presentation depending upon the disease severity. Knowledge of the spectrum of presentation of hemophilia in the local population helps in early diagnosis and planning of management.

Although ecchymoses and hemarthrosis were the leading clinical manifestations of hemophilia in children, in the present setting, posttraumatic bleeds and gum bleeds were the main features at the onset of presentation of these children. So, presence of these features in an otherwise normal child should be considered for the evaluation of hemophilia. Bleeding manifestations in newborn mimicking

Vitamin K deficiency warrant more vigilance for detection of hemophilia in the neonatal period, especially for ICH which results in high mortality and morbidity. Promotion of regular availability of factor concentrate, prophylactic factor replacement, establishment of hemophilia center with comprehensive care, regular training of medical and paramedical staff, and positive public awareness through media such as radio, television, and magazines in our settings will help in achieving the outcome comparable to developed countries. All patients had negative screening tests for transfusion-transmitted infections emphasizing the safety of plasma products after 1996.

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Conflicts of interest

There are no conflicts of interest.

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