HAEMOPHILIA B: CLINICAL MANIFESTATIONS AND COMPLICATIONS

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ABSTRACT

Background: Haemophilia B is X-linked recessive inherited disorder of factor IX deficiency. It is classified as severe, moderate and mild depending upon plasma levels of factor IX. The development of inhibitors is seen during treatment of haemophilia B against F-IX. This study was aimed to determine the frequency of different complications in haemophilia B patients.

Patients and Methods: Total 45 patients of Haemophilia B already enrolled in the Haemophilia society of Pakistan Lahore chapter were included in this study. Clinical history and physical examinations were recorded on a pre designed proforma. Laboratory testing for establishment of diagnosis of haemophilia B and inhibitors of FIX was done.

Results: Out of 45 patients, 10 (22.2%) had severe disease while 28 (62.2%) had moderate and 07 (15.6%) had mild disease. Twenty nine (64.4%) of patients with severe and moderate disease were diagnosed below 5 years of age while none with mild disease was diagnosed under 5 years of age. Arthropathy was the most frequently developing complication in patients 10 (100%) of severe Hemophilia B. Post circumcision bleeding was found to be the most common first episode of bleeding in patients of haemophilia B 29 (64.4%). Inhibitor against F-IX developed in only one patient of severe disease 1 (10%).

Conclusion: Arthropathy is the commonest complication and circumcision is the first bleeding site in most of the haemophiliacs.

Key Words: Haemophilia B, Factor IX, Inhibitors.

INTRODUCTION

Haemophilia is the most severe inherited bleeding disorder (INB). It affects individuals from all geographical areas with same frequency.[1] Haemophilia A and B are X-linked disorders which result in deficiencies of the anticoagulation activity of clotting factors VIII (FVIII) and IX (FIX) respectively. Haemophilia B is also referred to as Christmas disease. Incidence of haemophilia B deficiency is approximately 1:25,000 – 30,000 male births.[2,3]

Classification of haemophilia is based on either clinical bleeding symptoms or on procoagulant factor levels. Patients having < 1% factor is defined as severe. Factor level in the range of 1 – 5% has been described as moderately severe and patients having factor levels 6% – 30% as mild haemophiliacs.[4,5] Bleeding episodes in severe haemophiliacs commonly occur in joints, muscle and soft tissue, skin, mucosa and occasionally in the brain and spinal cord. Recurrent joint bleeding frequently leads to chronic synovitis and secondary arthropathy, resulting in long – term morbidity and severe physical impairment.[6] Correct diagnosis of haemophilia B depends on availability of screening coagulation tests (APTT, PT) correction studies and finally one stage APTT based assay of the deficiency factors to assess the severity of the disease.[7]

Transfusion – transmitted infections (TTI) are serious complications of Haemophilia patients treated by factor concentrates. Multi – transfused haemophiliacs are endangered of acquiring viral hepatitis due to the fact that concentrated coagulation factors are prepared from plasma of thousands of blood donors.[8] The development of inhibitors is the most serious complication of haemophilia. Patients who develop an inhibitor have far more severe, disease course than the patient without inhibitors.[9] Factor IX inhibitors are far less common (occurring in 2 – 3% of boys with haemophilia) B than haemophilia A, but they are accompanied by the occurrence of anaphylaxis or severe allergic reactions to any factor IX – containing product.[10] Screening for inhibitors is normally conducted by Bethesda – based method.[11] Clinical and laboratory data from haemophilia treatment center in Lahore is presented with the purpose to gather and propagate information regarding, clinical manifestation, time of presentation and potentially life – threatening complication in association with severity of haemophilia B. This might help to facilitate new diagnostic and therapeutic strategies for haemophilia B patients.

PATIENTS AND METHODS

Patients reporting to Haemophilia Welfare Associ-

ation Lahore were included in this study. In a total of 349 patients 45 were diagnosed as Haemophilia B during the period of 2005 to 2008. For each of these patients all available information including previous medical records was obtained. Patients and parents were also interviewed to supplement information. Detailed questionnaire was filled by each patient in which information was taken regarding, the age of the onset of bleeding, duration of bleeding with its frequencies / year, past history of blood transfusion and the nature of bleeding manifestation (bleeding with dental procedures or after trauma) and history of drug or factor IX concentrate intake. Complications of disease like arthropathy, joint deformities, CNS complications, hepatitis B, C and HIV infection were also noted.

Venous blood samples from each patient was withdrawn after written consent and divided into two tubes containing trisodium citrate 3.2 g/dl at a ratio of 9:1. Blood samples were centrifuged at 2000 g for 15 minutes to obtain platelet poor plasma (PPP) to perform coagulation studies. This included activated partial thromboplastin time (APTT), mixing studies using aged and adsorbed plasma, Factor IX assay and inhibitor screening. Mixing studies were done by measuring APTT after making 1:1 ratio of patient's plasma with aged and absorbed plasma. Measurement of factor IX levels was done to classify the patients in severe, moderate and mild category by one – stage assay method. The assay was performed on serial dilutions of the patient's plasma with factor deficient plasma. The inhibitors screening for FIX was done by performing an APTT on a mixture of equal volume (1:1) of patients' plasma and normal pool plasma after 2 hours of incubation at 37°C. Presence of an inhibitor was confirmed by the prolonged APTT after 2 hrs incubation as compared to controls without inhibitor. In a person with haemophilia B, a prolonged APTT of a mixture of patient and normal plasma strongly suggests the presence of an inhibitor to the clotting factor IX.

All the patients had normal Prothrombin time (PT), Platelet count and Bleeding time (BT) but the activated partial thromboplastin time (APTT) was prolonged. In mixing studies Haemophilia B patients showed no correction of APTT by addition of adsorbed plasma but were corrected by aged plasma. Factor IX levels were decreased to 30% or less in all patients of haemophilia.

Statistical Analysis

The data was entered and analyzed using SPSS 18.0. Qualitative variables were expressed as percentages and frequencies. Pearson chi square test were applied to observe association between qualitative variables. A p-value of < 0.05 was considered as statistically significant.

RESULTS

Total 45 patients were included in this study. Ten patients (22.2%) had severe disease while 28 (62.2%) had moderate and 07 (15.6%) were mild category on the basis of factor IX levels. Consanguinity was seen in 62% and majority 32 (71%) out of 45 had family history of haemophilia in siblings, maternal uncles and cousins. p value was found to be statistically significant < 0.05 (Table 1).

Factor level was found to be associated with age of presentation of the disease. Most of the patients with severe disease presented below the age of five years. All (n = 10) of the patients with severe disease (Factor IX < 1%) presented at less than five years of age. Patients (n = 07) with mild disease (factor IX 6-30%) presented after five years of age (Table 2).

Complications like arthropathy, transfusion transmissible diseases were observed more in patients having severe and moderate disease. Arthropathy was the most frequently occurring complication in all of these patients. In patients having severe disease, 100% were diagnosed with arthropathy while same complication was seen in 71.4% and 28% of patients with moderate and mild disease respectively (Table 3).

Infection with hepatitis C were also observed in patients with severe 3 (23%) and moderate 7 (54%) and mild 3 (23%) haemophiliac patients. Only one patient in severe disease develops inhibitor against factor IX, None of the patients diagnosed with moderate and mild haemophilia developed inhibitors (Table 3).

Orthopedic complications observed in patients with haemophilia are listed in Table 4. The most commonly involved joint was

Table 1: *Demographic data of patient with Haemophilia B.*

	Number of Patients	*Percentage*	*P-value*
Severity of disease			
Severe	10	22.2%	< 0.05
Moderate	28	62.2%	
Mild	07	15.6%	
Family History			
Positive	32	71%	< 0.05
Negative	13	28%	
Marital Status			
Cousin marriage	28	62%	< 0.05
Not related	10	22%	
Unknown	7	15%	

found to be knee 15 (33.3%). Single joint involvement was found in 31 (68.5%) of patients and multiple joints involvement was seen in 4 (8.8%) patients (Table 4).

Another important clinical manifestation of haemophilia B had been bleeding from various sites. First bleeding episode occurred after circumcision in 7 (70%) of patients with severe disease as compared to 20 (71.1%) and 2 (28.5%) of patients in moderate and mild diseases respectively. Prolonged bleeding after injury, spontaneous bleeding and easy bruising were slightly more in patients with moderate disease (Table 5).

Frequency of bleeding episodes was variable amongst patients with different factor levels. All of the patients with severe disease reported higher number of bleeding episodes as compared to patients with mild disease (Table 6).

Table 2: *Association of severity of disease with age of presentation.*

Age of Presentation	*Severe FXI Level < 1% (n = 10)*	*Moderate FXI Level 1 – 5% (n = 28)*	*Mild FXI Level 6 – 30% (n = 7)*
≤ 1 year	3 (30%)	02 (7.14%)	Nil
1 – 5 years	7 (70%)	17 (50.7%)	Nil
> 5 years	Nil	09 (32.4%)	07 (100)

Table 3: *Severity of disease with development of complications.*

Type of Complication	*Severe FXI Level < 1% (n = 10)*	*Moderate FXI Level 1 – 5% (n = 28)*	*Mild FXI Level 6 – 30% (n = 07)*
Arthropathy	10 (100%)	20 (71.4%)	02 (28%)
Inhibitor	01 (10%)	Nil (0%)	Nil
HBV infection	Nil	02 (0%)	Nil
HCV infection	03 (23%)	07 (54%)	03 (23%)

DISCUSSION

Due to considerably lower incidence of haemophilia B, it has consequently received less attention in the research literature. Generating information in our local population regarding the key clinical features and complications in patients with haemophilia B will be fundamental for supporting improvements in caring for such patients.

In this study we found 22.2% of patients having haemophilia B had severe disease, 62.2% were diagnosed to have moderate and 15.6% had mild disease. Observation different from our results were obtained in a previous study carried out in six states of USA showing 43% had severe haemophilia B, while 25.6% had moderate and 32% had mild disease.[12] In another study in Iran, it was shown that severe disease was found in 48% of patient, moderate in 37.7% and mild type in 16.5% of haemophilia B patients.[13] Variations in prevalence rates and disease severity in our population could be due to geographic difference. Factors that may have contributed to the geographic differences include variations in case finding and dissimilar diagnostic methodologies due to a lack of standardized laboratory testing.[12]

Consanguinity and family marriages among parents (62%) were important finding in our study. Haemophilia B is transmitted through a wide range of genetic defects, with most affected families having their own unique mutation.[2] Family history of bleeding was present in 71% of patients in our study while only

Table 4: *Orthopedic complications in patient with Haemophilia B.*

Involved Joint	*Number of Patients*	*Percentage*
Multiple joint involvement	04	8.7%
Absent	10	22.2%
Knee joint	15	33.3%
Elbow	08	17.7%
Hip	02	4.5%
Ankle Joint	06	13.3%

Table 5: *Association of severity of disease with first bleeding site.*

Initial Site of Bleeding Episode	*Severe FXI Level < 1% n = 10*	*Moderate FXI Level 1 – 5% n = 28*	*Mild FXI Level 6 – 30% n = 07*
Circumcision	07 (70%)	20 (71.4%)	02 (28.5%)
Spontaneous	01 (10%)	01 (3.6%)	Nil (0%)
Easy bruising	Nil	02 (7.2%)	01 (14%)
Injury	Nil	05 (17.8%)	04 (57.5%)
Umbilical Stump	02 (20%)	Nil	Nil

29% showed no family history of bleeding. It has also been observed previously that nearly one third of cases of haemophilia occur with no preceding family history and they possibly develop disease from new genetic mutations.[14] Older studies give varying estimates of upto 50% positive family history in severely affected cases of haemophilia.[15]

In our study we found variable results showing association of frequency of bleeding episodes with concentration of factor IX levels. In patients with severe haemophilia 1 – 3 bleeding episode per month occurred in 80% while rest showed more than 3 bleeding episodes. Whereas all the patients with mild disease exhibited less than 1 bleeding episode per month. It has been shown in previous study that 53.5% of patients with severe haemophilia had greater than 25 episodes per year.[15] It has also been reported earlier that spontaneous bleeding is uncommon in moderate haemophilia and mild haemophilia may present with abnormal bleeding after surgery, tooth extraction, or major injuries.[16]

The most common complication observed in our patients was arthropathy; all of patients with severe disease, 71% with moderate disease and 28% with mild disease were suffering from this complication which is in accordance to previous findings that 75% of bleeding episodes occur in joints. While haemophilic arthropathy was found to be uncommon in a study carried out in paediatric population in Egypt. This may be because that this complication is uncommon in young children and due to high intensity of replacement therapy satisfactory results of orthopedic status of severe haemophilic patients were observed.[1] Joints which are most commonly effected in decreasing order were, knee, elbow, ankle and shoulder.[3,15] Comparable results were also demonstrated in our study.

In the present study 23% severe haemophiliacs were positive for HCV but seropositivity for HCV was higher 54% in patient with moderate haemophilia. In a study conducted in India the seropositivity for anti-HCV in haemophiliacs was found to be 25%. In the same study it was also noted that Anti-HCV positivity was not related to the age of the subject or number of blood components transfused.[13] Another study results revealed that 38.7% patients with Haemophilia A or B were seropositive for HCV, while conversely, seropositivity for HBV and HIV was significantly lower.[8] Similar results were also demonstrated in our study. To minimize the risk of post transfusion hepatitis in high risk recipients like recipients like transfusion dependent haemophiliacs screening of HBV and HIV status should be a prerequisites.

Factor IX inhibitors are much less common in patients with haemophilia B than in patients with haemophilia A.[17] Inhibitors occur in 20 – 30% of patients with haemophilia A but in only 5% of patients with haemophilia B.[11] However in our study only 1 (10%) patient of severe haemophilia B developed inhibitors while patients having mild and moderate disease did not show any inhibitors. It is previously reported that prevalence of inhibitors in severe haemophilia B is about 4% and inhibitors arise much more commonly in severe haemophilia than in mild or moderate haemophilia.[18] Although the incidence of inhibitors in patients with haemophilia B is low but most patients who developed inhibitor had "high titre". The presence of certain mutations in the patients FIX gene is an important predisposing factor in the development of inhibitors. Mutations resulting in a loss of coding information are most frequently associated with inhibitor development. The development of inhibitors in haemophilia A and B reflect the type and severity of haemophilia, the regime of factor concentrate replacement (prophylactic or on demand). Inherited factors, positive family history and environmental factors.[19]

Table 6: *Association of severity of disease with bleeding episode per month.*

Bleeding Episodes / Month	*Severe FXI Level < 1% n = 10*	*Moderate FXI Level 1 – 5% n = 28*	*Mild FXI Level 6 – 30% n = 07*
< 2 times	Nil	17 (61%)	07 (100%)
1 – 3 times	08 (80%)	11 (39%)	Nil
> 3 times	02 (20%)	Nil	Nil

It is *concluded* that Arthropathy is the most common complication developed in patients of Haemophilia B while circumcision was the major site of first bleeding episode.

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REFERENCES

1. Tonbary Y, Elashry R and Zaki MES. Descriptive Epidemiology of Haemophilia and Other Coagulation Disorders in Mansoura, Egypt. Retrospective Analysis. Medit J Hemat Infect Dis 2010: Vol. 2 (3).
2. CME. Haemophilia. June 2004; Vol. 22 (6): P. 355-356.
3. Mahalangu JN and Gilham A. Guideline for the Treatment of Haemophilia in South Africa. S Afr Med J 2008; 98: 125-140.
4. Nawaz N, Hussain R, Masood K and Niazi G. Molecular Basis of Haemophilia B in Pakistan: Identification

of Two Novel Mutations. World Journal of Medical Sciences 2008; Vol. 3 (2): 50-53.
5. White GC, rosendaal F, Aledort LM, Lusher JM, Rothschild C and Ingerslev J. Definitions in Haemophilia Recommendation of the Scientific Subcommittee on Factor VIII and Factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost 2001; 85: 560.
6. Stieltjes N, Torchet MF, Misrahi L, Robert VR, Lambert T, Gueroise C and et al. Epidemiological survey of haemophiliacs with inhibitors in France: orthopaedic status, quality of life and cost. Blood Coagulation and Fibrinolysis 2009; 20: 4-11.
7. Ghosh K, Shetty S and Ghosh K. Haemophilia: A High Cost Low Volume Disease: Suitable Preventive Strategies for Developed Countries. The Open Hematology Journal, 2008; 2: 20-24.
8. Zhubi B, Mekaj Y, Baruti Z, Bunjaku I and Belegu M. Transfusion transmitted infections in haemophilia patients. Bosnian journal of basic medical sciences 2009; 9 (4): 271-277.
9. Berntorp E, Shapiro A, Astermark J, Blanchette VS, Collins PW, Dimichele P, Escuriola C and et al. Inhibitor treatment in haemophilias A and B: summary statement for the 2006 international consensus conference. Haemophilia 2006; 12 (Suppl. 6): 1-7.
10. Lusher JM. Inhibitors in young boys with haemophilia Baillie Ä re's Clinical Haematology 2000; Vol. 13, No. 3: Pp. 457-468.
11. Hay CRM, S, Collins BPW, Keeling DM and Liesner R. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. British Journal of Haematology, 2006; 133: 591-605.
12. Bhattacharya DK. Haemophilia in the Indian Scenario. Int J Hum Genet 2006; 6 (1): 33-39.
13. Torghabeh HM, Pourfathollah A, Shooshtari MM, and Yazdi ZR. Relation of Factor VIII and IX Inhibitors with ABO Blood Groups in 150 Patients with Haemophilia A and B. Iran J Allergy Asthma Immunol March 2006; 5 (1): 33-34.
14. A. Jamil, M. Bayoumy, D. Irum and B, Adler. Peadiatrics severe haemophilia: Initial presentation, characteristics and complications. The internet journal of Haematology. 2004: 1 (2).
15. Haemophilia B (F9). Sequencing to determine the causative factor IX mutation in affected individuals and carrier status in at – risk individuals. National reference laboratory, ARUP laboratories; 2009: www.arupconsult.com.
16. Philipp C. The Aging Patient with Haemophilia: Complications, Comorbidities, and Management Issues. American Society of Hematology 2010: P 191-196.
17. Kasper CK. Diagnosis and Management of Inhibitors to Factors VIII and IX An Introductory Discussion for Physicians. Treatment of Haemophilia: Sep 2004: (34).
18. Chitlur M, Warrier I, Rajpurkar M and Lusher JM. Inhibitors in factor IX deficiency a report of the ISTH-SSC international FIX inhibitor registry (1997-2006). Haemophilia; 2009: 1-4.