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Original Research Article

A Study on Variances in the Reported Haemophilia Prevalence Throughout the Bihar Region in Tirhut

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Abstract

Aim: Study of variations in the reported haemophilia prevalence around the Bihar Region in Tirhut.

Methods: The present Observational study was conducted in the Department of General Medicine, Shri Krishna Medical College and Hospital, Muzaffarpur, Bihar, India for 1 year. Patients with clinically suspected bleeding disorder, who were referred to us either from departments of our tertiary care hospital or from Hemophilia Society were included in this study. Complete Blood Count (CBC), General Blood Picture (GBP), tests for coagulation: Prothrombin time (PT), Activated partial thromboplastin time (APTT), Thrombin time, Correction experiment to know the specific factor deficiency or inhibitors present by Normal Plasma, Normal aged serum, $Al(OH)_3$ adsorbed plasma, Specific Factor Assay, Inhibitor Assay.

Results: 100 patients diagnosed as suffering with Hemophilia A or B were included in study. The age of patients ranged from 3 months to 50 years. In our study, maximum number of patients was in age group 10-15 years. All patients were male. In our study, family history was present in 64% of patients, consanguinity was present in 5% of patients, 3% consanguineous patients were positive for family history. In our study, most common presenting clinical feature was prolonged bleeding after cut (79%). More than 3 joints were involved in 22% of haemophilia-A patients. Arthropathy/deformity was present in 19% of patients. Bilateral knee joints were involved in 15% of Hemophilia B patients. Arthropathy/deformity was present in 8% of patients. The mean for PT was 15.06 ± 1.06 while mean for APPT was 81.33 ± 19.20. Out of 100, 86(86%) were Haemophilia A and 14 were (14%) Hemophilia-B patients. The Mean Factor VIII value was 48.58 ± 29.33 (*P* value < 0.001). Factor IX assay was done in 50 patients. Mean Factor IX value was 109.60 ± 23.93 (*P* value < 0.001). 58.14% patients of Haemophilia A were having <1% factor VIII concentration. In our study 71.43% cases of Haemophilia B were having <1% factor IX. 37% patients were having transfusion ≥3 times, 38% were having <3 times. 4% cases of treated Hemophilia A patient develop inhibitor.

Conclusion: The prevalence of hemophilia and incidence of inhibitors in these patients is varies in different regions of India. This variation may be due to the type of product used as treatment, intensity of treatment or the genetic characteristics of the patients.

Keywords: Hemophilia.

Introduction

Deficiency of factor VIII (Hemophilia A), factor IX (Hemophilia B) and Von Willebrand's factor are the most frequent coagulation defects. Hereditary deficiencies of other coagulation factors are significantly less common[1]. In geographic or ethnic populations where consanguineous unions are common, recessively inherited bleeding disorders are more common. Hemophilia A occurs in 1 out of 10,000 male births, while hemophilia B, occurs in 1 out of 30,000 male births. The prevalence of haemophilia A varies with the reporting country, with a range of 5.4-14.5 cases per 100,000 male individuals[2,3].

The most serious complication of replacement therapy in hemophilia is the development of inhibitors[4]. An inhibitor is a polyclonal high-affinity immunoglobulin G (IgG) that is directed against the FVIII protein. These antibodies can be either inhibitory or non inhibitory. Factor VIII have different types of domains. Antibody binding at these domains results in functional impairment of factor VIII. Development of these antibodies leads to an increase in the management cost, morbidity and mortality. The incidence of inhibitors in patients of factor VIII deficiency varies in different regions of India. This variation may be due to the type of product used as treatment, intensity of treatment or the genetic characteristics of the patients[5,6]. Antibodies to factor IX are rare in comparison to factor VIII and seen only in 1-3% of hemophilia B patients. The data related to the inhibitors and prevalence of hemophilia are lacking from this part of country.

Material and methods

The present Observational study was conducted in the Department of General Medicine, Shri Krishna Medical College and Hospital, Muzaffarpur, Bihar, India for 1 year. after taking the approval of the protocol review committee and institutional ethics committee.

Methodology

Patients with clinically suspected bleeding disorder, who were referred to us either from departments of our tertiary care hospital or from Hemophilia Society. For this purpose, an informed consent was made and detailed performa containing the nature of bleeding episodes, age of onset, frequency of bleeding, family history, mode of inheritance and history of prior medications including blood transfusion was taken along with detailed physical examination. The following Investigations were done for hemostatic assessment: Complete Blood Count (CBC), General Blood Picture (GBP), tests for coagulation: Prothrombin time (PT), Activated partial thromboplastin time (APTT), Thrombin time, Correction experiment to know the specific factor deficiency or inhibitors present by Normal Plasma, Normal aged serum, $Al(OH)_3$ adsorbed plasma, Specific Factor Assay, Inhibitor Assay. All the tests were performed within 4 hours of blood collection. However, factor VIII assays were done after 1 or 2 days, for that plasma was stored at -20 to -30 degrees centigrade. The Bethesda assay is used to quantify the concentration of factor VIII inhibitor. Test plasma is mixed with a source of Factor VIII and is incubated for 2 hours at 37°C.

A control mixture is prepared by mixing Factor VIII deficient plasma and buffered-normal plasma pool and is also incubated. After 2 hours the Factor VIII activity of each mixture is measured. The Factor VIII of the test mixture is compared to that of the control and the percentage of residual Factor VIII is calculated. One Bethesda unit (BU) is defined as that amount of inhibitor in the test plasma (patient) that results in 50% residual Factor VIII activity. Dilutions of patient plasma are also tested. A patient plasma producing a residual Factor VIII activity of 50% in an incubation mixture is considered to contain one Bethesda unit per mL. Relationship between the residual factor VIII activity in normal plasma and the inhibitor activity of

the test plasma can be read off this plot. At 50% inhibition, the test plasma contains, by definition, 1 Bethesda inhibitor unit per ml. Note that the y-axis is a logarithmic scale.

Statistical analysis

Statistical analysis was done using SPSS 24.0. For categorical variables, Chi square test and Fisher's – exact test were used.

Results

100 patients diagnosed as suffering with Hemophilia A or B were included in study. The age of patients ranged from 3 months to 50 years. In our study, maximum number of patients was in age group 10-15 years. [Table 1] All patients were male. In our study, family history was present in 64% of patients, consanguinity was present in 5% of patients, 3% consanguineous patients were positive for family history. In our study, most common presenting clinical feature was Prolonged bleeding after cut (79%) [Table 2]. More than 3 joints were involved in 22% of haemophilia A patients. Arthropathy/deformity was present in19% of patients. Bilateral knee joints were involved in 15% of Hemophilia B patients. Arthropathy/deformity was present in 8% of patients. The mean for PT was 15.06 ± 1.06 while mean for APPT was 81.33 ± 19.20. Out of 100, 86(86%) were Haemophilia A and 14 were (14%) Hemophilia B patients. The Mean Factor VIII value was 48.58 ± 29.33 (*P* value < 0.001). Factor IX assay was done in 50 patients. Mean Factor IX value was 109.60 ± 23.93 (*P* value < 0.001). 58.14% patients of Haemophilia A were having <1% factor VIII concentration. In our study 71.43% cases of Haemophilia B were having <1% factor IX. [Table 3]. 37% patients were having transfusion ≥3 times, 38% were having <3 times. 4% cases of treated Hemophilia A patient develop inhibitor.

Table 1: Age distribution of patients (*n*=100)

Age in years	No.	Percentage
Below 1	8	8
1-5	18	18
5-10	11	11
10-15	25	25
15-20	14	14
20-30	20	20
Above 30	4	4
Total	100	100

Table 2: Frequency of bleeding symptoms in patients (*n*=100)

Clinical Symptoms	No. of Patient	Percentage (%)
Prolonged bleeding on cut/trauma	79	79
Ecchymosis/bruise	46	46
Haemarthrosis	41	41
Haematoma	30	30
Petechiae	13	13
Epistaxis	9	9
Gum bleeding	9	9
Bleeding after tooth extraction	4	4
Bleeding after tonsillectomy	3	3
Post-circumcission bleeding	3	3
Umbilical bleeding	3	3
Haematuria	2	2
Haematemesis	1	1

Table 3: Factor VIIIc and Factor IX concentration in Haemophilia A and Haemophilia B patients

Factor VIII concentration (%)	Number	Percentage (%)
<1	50	58.14
1-5	16	18.60
5-50	20	23.26
Factor IX concentration	**Number**	**Percentage (%)**
<1	10	71.43
1-5	3	21.43
5-50	1	7.14

Discussion

In the present study, a total of 100 patients with abnormal bleeding manifestations were investigated. Amongst these, 86% was suffering from Hemophilia A, whereas 14% from Hemophilia B. In our study, maximum number of patients was in age group 10-15 years. Mean age was 12.25 ± 8.84, median age of the patients was 10 years and the most frequent age i.e., mode was 15 years. In a study done by Gupta et al. the age at presentation ranged from 2-47 years with a median age of 32.2 years[7]. Sajid et al. reported the age at presentation ranged from 3 to 57 years with a median age of 17 years. Mostly patients with mild deficiency presented and diagnosed in adult group[8]. Munira et al. reported mean age of 15.8 years[9]. All patients in the present study were male. As Haemophilia A and B are X-linked disorders, it most commonly affects males, female act as carrier. In the present study, most common presenting clinical feature in was prolonged bleeding after cut (79%) >Ecchymosis/bruise (46%) >Haemarthrosis (41%) >Haematoma (30 %) >Pete chiae (13 %) >Epistaxis (9%) and Gum bleeding (9%)

>Bleeding after tooth extraction (4%) >Bleeding after tonsillectomy (3%) >Post circumcision bleeding (3%) >Umbilical bleeding (3%) >Haematuria (2%) and least common Haematemesis (1%). Ahmed et al. reported most common presenting feature in hemophilia as hemarthrosis (82%)[10]. Munira Borhany et al. reported Haemarthrosis in 72.85%, Haematoma (51.4%), post circumcision bleeding (37.14%), Bleeding after trauma (28.51%) followed by haematuria, bruise, gum bleeding[9]. In the present study, 41% have experienced joint swelling at least once in life involving one, two or multiple joints, most commonly knee joint. Sajid et al. also reported knee joint as most common joint involvement (48%) and in 36% more than one joint was involved[8]. 58.14% cases of hemophilia A were having <1% factor VIIIc designated as severe hemophilia A, 18.60% were having 1-5% factor VIIIc designated as moderate hemophilia A and 23.26% were having > 5% factor VIIIc designated as mild hemophilia A. In a study by Ahmed et al. 77.8% cases of severe hemophilia A. 14.4% of moderate hemophilia A, and 7.75% cases of mild hemophilia A were reported[10]. Sajid et al. reported 37.2% (79) mild, 41% (87) moderate, 21.6% (46) severe Haemophilia A out of 212 patients of Haemophilia A.[8] These data are comparable with clinical presentation of the patients. Patients having very less concentration of factor VIIIc presented to clinics due to very severe symptoms, while patients with mild to moderate factor VIIIc deficiency did not came to clinics because symptoms were less server and managed locally. In present study, 71.43% cases of hemophilia B having <1% factor IX designated as severe hemophilia B, 21.43% cases of hemophilia B were having 1-5% of factor IX designated as moderate hemophilia B, and 7.14% cases were having 5-50% of factor IX concentration designated as mild

hemophilia B. In the study of Ahmed et al., hemophilia B patients have 69.6% severe, 19.2% moderate and 11.2% mild disease[10]. Haemophila can be referred to as a disorder that causes joint damage leading to limitation in conducting daily activities and changes in social functioning. In the developed countries haemophiliacs have a quality of life very similar to that seen in general population due to provision of safety factor concentrates and multidisciplinary comprehensive care approach, but in countries like ours, hemophiliacs' are not treated with safe products and appropriate qualities of the products because of cost related issues, so lack of adequate treatment can result in pain, arthropathy and disability. Although hemarthrosis was the leading cause of presenting feature of the haemophilia in children in the present setting, bruises and hematoma either spontaneous or traumatic were the main features at very onset of presentation of these children. So, the presence of these features in an otherwise normal child should be considered for evaluation of hemophilia.

In the present study, we found factor VIII inhibitor in only 4% treated patients. One of the patients had inhibitor titre of 8BU, and the other had 4BU. Wight and Paisley, reported an overall inhibitor prevalence of 5-7% and when limited to patients with severe disease is much higher at 12-13%.[11] Lusher et al. reported incidence of new factor inhibitor in patients with severe factor VIII deficiency is approximately 30%. About 60% of those inhibitors are of high titer (>5BU) and remaining (40%) are of low titre (<5BU).[12] Most factor VIII allo antibodies are directed against epitopes in the A2 and A3-C1 domain of factor VIII, or auto antibodies, those that suddenly appear in person with normal factor VIII gene and previously normal plasma level of plasma factor VIII, causing acquired hemophilia[13-15]. Factor affecting development of inhibitor classified as non-modifiable and modifiable. Non-modifiable risk factors include high risk hemophilia genotype, co-stimulatory genotype-immuno genotype interaction, ethnicity and positive family history. Modifiable risk factors include environmental influence that is implicated in increasing the risk of inhibitor formation. Environment factors include age at start of prophylaxis, type of replacement therapy product and intensity of treatment[16]. In India, for hemophilia, inhibitor screening and other genetic test are not available therefore the identification and management of these patients is difficult.

Conclusion

The prevalence of hemophilia and incidence of inhibitors in these patients is varies in different regions of India. This variation may be due to the type of product used as treatment, intensity of treatment or the genetic characteristics of the patients.

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