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A PILOT STUDY ON THE DEVELOPMENT OF INHIBITORS IN HAEMOPHILIA PATIENTS.

Medical Science

Priyanka Chauhan Senior Resident,PDCC,SGPGIMS Lucknow

Meenakshi Pathak* Assistant Professor, F H Medical College,Tundla Firozabad*Corresponding Author

Sunit Pathak Associate Professor, F H Medical College,Tundla Firozabad

ABSTRACT

Aim: To estimate the prevalence of inhibitors in hemophilia A and B.

Material and methods: Out of 81 haemophilia patients screened, 73 (90%) had haemophilia A and 8 (10%) had haemophilia B. The age range of patients with haemophilia A was 7-46 years (mean age, 19.19 years) and that of haemophilia B was 8-20years (mean age=13 years). Most patients presented with hemarthroses. . Bethesda assay was performed to quantify the inhibitors in these haemophilia A patients [Table 2].

Results: Twelve patients (16%) of haemophilia A were positive on inhibitor screening using the mixing study which is comparable to other studies in IndiaOnly two patients showed high titre levels (>256 BU/ml). None of Haemophilia B patients tested positive for inhibitors. In this study all the patients who developed inhibitors had severe hemophiliaA .

Conclusion: Further studies are required in our country to derive a robust set of data regarding prevalence of inhibitors in haemophilia patients so that appropriate treatment protocols can be institutionalised.

KEYWORDS

inhibitors,haemophilia A,Bethesda assay

INTRODUCTION

Haemophilia A and B are X-linked inherited bleeding disorders characterized by a deficiency of functional clotting factor VIII and IX respectively.

Management of bleeding episodes in patients with haemophilia A and B consists of administering FVIII and FIX concentrates derived from plasma or recombinant factors. The development of antibodies against these factors is a major clinical complication as these inhibitory antibodies bind to infused FVIII, FIX, thereby reducing their half life and neutralizing its coagulant activity [2] . Inhibitors are estimated to occur in 20%–35% of patients with severe haemophilia A [1,3] and 1.5-3% of haemophilia B patients [4].

It is generally accepted that inhibitor screening should occur before invasive procedures and at regular intervals during the initial 50 treatment days, as this is the highest risk period for inhibitor development [5].

This study was conducted with the aim of assessing the prevalence of inhibitors in haemophilia A and haemophilia B patients from our hospital as there is limited data in this context from the developing countries.

MATERIALAND METHODS

This study was conducted in the Department of Paediatrics, Sarojini Naidu Medical College, Agra, Uttar Pradesh (India). Out of a total of 185 haemophilia patients registered in our institution, 7 were previously diagnosed with inhibitors, remaining 178 patients were contacted through telephone to take part in the study and date and time of testing was conveyed to them. Only 81 patients of moderate (10%) and severe (90%) haemophilia A and B turned up and were enrolled in the study. Citrated and ethylenediamine tetra acetic acid (EDT A) samples were collected from the patients and their clinical details were recorded. Prothrombin time (PT), Activated partial thromboplastin time (APTT), Factor VIII and IX assays and Bethesda assay for inhibitors was done on citrated plasma. The clinical profile, exposure to haemophilia factors and the laboratory results were recorded. The categorical data was expressed as frequency and percentage and continuous data was expressed as mean and standard deviation.

RESULTS

Out of 81 haemophilia patients screened, 73 (90%) had haemophilia A and 8 (10%) had haemophilia B. The age range of patients with haemophilia A was 7-46 years (mean age, 19.19 years) and that of haemophilia B was 8-20years (mean age=13 years). Most patients presented with hemarthroses, with knee joint (39%) followed by elbow joint (26%) and ankle joint (21%) being the most commonly involved sites, remaining 14% presented with either bleeding from trauma site, gum bleed or muscle bleed In the coagulation profile of haemophilia A patients [Table 1], range of APTT was 35-139.1 seconds (normal control = 30.9 seconds; mean, 79.94 seconds) and in haemophilia B patients range of APTT was 88.3-118.6 seconds (normal control =30.6 seconds, mean 101.58 seconds). Factor VIII levels were in the range of <1% to 3.80% (median < 1%) and Factor IX levels were <1% in all 8 patients of Haemophilia B. Based on factor levels , the patients were categorized as follows: moderate haemophilia 8(10%); and severe haemophilia 73 (90%). Twelve patients (16%) of haemophilia A were positive on inhibitor screening using the mixing study. Bethesda assay was performed to quantify the inhibitors in these twelve haemophilia A patients [Table 2]. Only two patients showed high titre levels (>256 BU/ml). None of Haemophilia B patients tested positive for inhibitors.

TABLE-1 Profile of haemophilia patients (n=31)

Parameter	Haemophilia A	Haemophilia B
Age (yrs) mean±SD	19.18±9.19	13±5.29
APTT (secs) mean±SD	79.94±22.44	101.58±13.87
Range	35-139.1	88.3-118.6
Factor VIII/IX (%) median	<1%	<1%
Range	<1%-3.80%	
Severity	Moderate-8(10%) Severe – 73 (90%)	Severe-8(100%)

TABLE-2 Profile of patients who tested positive for inhibitors (n=12)

Patient number	Age (years)	APTT (secs) Control=30.9	Factor VIII (%)	Inhibitor level (BU/ml)	Exposure to factors (yrs)	Exposure days
1	7	82.2	<1	2	6.5	36
2	16	68.4	<1	4	12	48
3	17	93.8	<1	2	16	96
4	20	77.4	<1	2	18.5	220
5	20	88.3	<1	>256	17	180
6	31	69.4	<1	5	26	289

7	8	82.3	<1	4	5	29
8	23	73.4	<1	>256	17	178
9	18	89.8	<1	2	16.5	192
10	9.5	91.6	<1	4	5	25
11	21	78.9	<1	4	15.5	165
12	10	82.3	<1	2	7	40

Mean exposure days among inhibitor positive patients was 124.8 whereas in inhibitor negative patients it was 103.5.

DISCUSSION

In our study we collected data on clinical profile as well as laboratory parameters like APTT, factor levels, inhibitor levels of haemophilia patients registered in our centre. It is essential to collect data about patients, their present clinical condition, and coagulation parameters with assessment of inhibitors for better planning and structuring of haemophilia services. On analyzing the coagulation factor levels, majority of the haemophilia patients were categorized as severe, followed by moderate, which is similar to other studies where the majority of patients had severe disease [6,7]. Among 185 patients of haemophilia enrolled at our centre the ratio of haemophilia A:B was found to be 7:1, whereas a ratio of 4.2:1 has been reported from another study in India.[9]. . Most patients presented with hemarthroses on majority of hospital visits, knee joint was most commonly involved followed by elbow and ankle joint. Data are limited on prevalence of inhibitors in patients with haemophilia in India. The prevalence of inhibitors in our study was 16% among the haemophilia A patients. Most of these patients were previously being managed with plasma-derived factor concentrates from the beginning of symptoms. There was no family history of development of inhibitors in any patient. None of the patients in our study received prophylactic administration of factors and no patient was treated aggressively during the onset of symptoms. The mechanism of FVIII inhibitor development remains unresolved and complicated because no single factor can be counted as responsible. It appears that severely affected haemophiliacs with gene inversions, deletions or stop codon mutations in the FVIII gene, generate inhibitors more often than those with missense mutations [10]. Studies in the Netherlands, Belgium and Germany indicate that the manufacturing process may influence inhibitor development [11, 12, and 13]. Other risk factors for development of inhibitors are African or Hispanic race, immunological factors like major histocompatibility (MHC) class II system and polymorphism of cytokines[17]. The treatment related factors include the age at first exposure, intensity of first exposure, severity of haemophilia, prophylactic administration of factors and use of plasma derived and recombinant factors [17]. The inhibitor prevalence in our study is comparable to that reported from other studies in India, which is 8.2-13%.[6,8] Similarly, in a study among Chinese haemophilia A patients treated only with plasma-derived FVIII, cryoprecipitate, or fresh frozen plasma (FFP), the overall prevalence of inhibitors was 3.9%.[14] However, the prevalence in patients of severe haemophilia A reported from developed countries is as high as 30%.[15] The cause for a comparatively low prevalence of inhibitors in our patients as compared with studies from developed countries may be due to delayed initiation of factor replacement therapy and use of plasma derived factors, limited availability of purified factor concentrates in government hospitals. This is in accordance with the findings of the CANAL study, in which the intensity of treatment was associated with a higher risk for inhibitors when compared to most of the other risk factors examined [16]. In our study, only two patients were found to have a high titre of inhibitors (>256BU/ml) and the rest ten had a low titre of inhibitors (<5 BU/ml).We did not find inhibitors in any of the 8 haemophilia B patients. In another study from India, out of 35 haemophilia B patients, only one patient developed an inhibitor [6]. Inhibitor prevalence of 1.5-3% has been reported for haemophilia B [4].

The main limitation of our study is the small sample size of patients and the lack of serial monitoring of inhibitor levels. It is imperative to increase knowledge about this disease in the patients as well as in the society as a whole. Lack of knowledge is also a reason that less studies are conducted in developing countries as in our study we informed 185 patients to participate in the study but only 81 turned up. Further studies are required in our country to derive a robust set of data regarding prevalence of inhibitors in haemophilia patients so that appropriate treatment protocols can be institutionalised.

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