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A study on the pattern of inhibitor development in people with haemophilia A from Upper Assam, India

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Abstract
Hemophilia is a X-linked recessive disorder of the coagulation cascade, that results in deficiency in clotting factors VIII and IX, with a prevalence of one in 5000 to one in 30,000 live births, in type A and B respectively. Factor replacement therapy remains the mainstay of treatment along with supportive measures but is often associated with development of alloantibodies against the transfused factors, resulting in suboptimal treatment response, resulting in more complications, increased expenditure and as a result compromising the quality of life.

Methodology: In this hospital based cross sectional observational study done at the Hemophilia treatment centre in Assam Medical College and Hospital, Dibrugarh, India, 95 patients with Hemophilia A were enrolled. After taking due consent, detailed history was obtained and relevant investigations such as APTT (activated pro-thromboplastin time), Mixing test and Bethesda Assay were done.

Results: Out of the 95 patients, 17.89% patients tested positive for inhibitors, with majority having severe disease (52.95%), followed by moderate disease (29.41%) and mild disease (17.64%). Five complications were reported in our study, with an exception of gum bleed, rest all were more in patients with inhibitors. The prevalence of inhibitors was found to be more among the recipients of recombinant product compared to plasma derived once. (58.82% vs 23.52%).

Conclusion: With all the data, we concluded that, prevalence of inhibitor was more in severe forms of the disease, complications were more in PwHA with inhibitors and recipients of recombinant product were more likely to have inhibitors. Our study showed that 17.89% (n=17) PwHA developed inhibitors, which was more in age group, severity and after surgical procedures. This emphasizes the need for regular factor assessment and inhibitor screening as 1/5th of our patients developed inhibitor of which majority patients have low titre at our treatment centre.

Keywords: Haemophilia A, inhibitors, disease

Introduction

Haemophilia is a rare X-linked disorder of the coagulation cascade that occurs as a result of deficiency of clotting factor VIII and factor IX due to mutation in the F8 gene (haemophilia A) and F9 gene (Hemophilia B) respectively. Haemophilia A is more common than haemophilia B, accounting for around 83% of cases worldwide, with an estimated incidence of around one in every 5000 live male births [1]. In India, haemophilia prevalence of all types and severities was reported to be 22,594 in a population of over 1.38 million in 2020 [1], and it is accounts for around 1 in 100,000 live male births [2]. However, haemophilia is known to be under-diagnosed in India. Recent estimates suggest that 85,000–100,000 people with haemophilia would be registered in the country's bleeding disorders registry if investigative techniques (i.e. coagulation laboratories) were more widely available.

The severity of haemophilia is classified according to residual factor activity levels and its presentation depends on the same. People with haemophilia may present with bleeding after trauma, but haemophilia is characterised by spontaneous bleeding into joints and muscles, particularly in its severe form. Recurrent bleeding into musculoskeletal structures may lead to development of target joints and painful haemophilic arthropathy. Pseudotumours may also develop as a result of untreated bleeds [4].

In the 1960s, the introduction of the transfusion of blood and blood products, such as fresh frozen plasma and cryoprecipitate, led to a dramatic improvement in treatment outcomes for people with haemophilia, but came at the cost of blood-borne infections such as hepatitis B and C and HIV [5], and associated chronic comorbidities and mortality [6, 7]. In the early 1980s, recombinant DNA technology enabled the production of recombinant FVIII and FIX, which not only reduced the number of infections but also allowed prophylaxis as a treatment modality [5]. Just like any other therapy, factor replacement therapy has its own shortcomings, the most important of which is the potential for development of inhibitory alloantibodies against FVIII and FIX, increasing morbidity and cost of care, and having a detrimental impact on quality of life [8, 9]. Clinical suspicion arises when there is an inadequate response to factor replacement therapy and can be confirmed by Bethesda assay. Depending on the titre of inhibitors, patients are further classified as high and low responders, for which the treatment protocol varies [10].

The World Federation of Hemophilia (WFH) recommends systematic surveillance for inhibitors for people with haemophilia A, particularly when patients are at their highest risk of developing them [11]. This risk period is during the first 20 exposures to clotting factor concentrates and up to 75 exposures [11, 12]. The majority of people with haemophilia in India are still treated on-demand and therefore do not receive treatment regularly. It is only recently that some haemophilia centres in India have started to offer low and intermediate dose prophylaxis [13]. It is important that we understand patterns of inhibitor development in our patient population. Gaining better insights into how this correlates with clinical parameters may help in being able to better manage this patient population.

This study looked at the pattern of inhibitor development in people with haemophilia A (PwHA) receiving treatment at the haemophilia treatment centre (HTC) of Assam Medical College and Hospital, Dibrugarh, in Northeast India. The study objectives were to estimate the prevalence of inhibitor development in PwHA attending the HTC and to ascertain any correlation between clinical profile and the development of inhibitors.

Methodology

Study design

We conducted a six-month, hospital-based, cross-sectional observational study among PwHA who were receiving treatment and were under follow up at the HTC, Assam Medical College and Hospital Dibrugarh. Of the 95 patients in our study, 4 patients were already known to have inhibitors. Our patient population is focused particularly on Upper Assam, Northeast India. Patients of all ages who had been clinically diagnosed with haemophilia A of all severities, confirmed by investigation, and those who were willing to give their consent to participate in the study were included. Patients with haemophilia B and other factor deficiencies were excluded.

Ethics

The study was approved by the ethics committee of Assam Medical College and Hospital, Dibrugarh. Written informed consent was taken from all study participants before they were enrolled in the study. Consent for participating children was given by their parents or guardians.

Methods

After taking informed consent, the data was collected from study participants with the help of a questionnaire by trained staff during regular visits in our weekly Haemophilia clinic every Saturday. on when their haemophilia was diagnosed, the nature and site of any bleeding experienced, age of diagnosis frequency of bleeding, family history of inhibitors, and details regarding FVIII infusion, including type of treatment product and frequency. All participants had a detailed physical examination. The assessment and physical examination involved calculating Annual Bleed Rate (ABR), Annual joint bleed rate (AJBR), Annual Target Joint Bleed Rate (AJBR), Haemophillia Joint Health Score (HJHS) and Functional Independence Score in Haemophilia (FISH).

Blood samples were collected for haemostatic assessment. The following tests were performed: prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time, mixing studies and inhibitor assay.

Sample collection and processing

10 cc blood was collected in 3.2% trisodium citrate vacutainers and centrifuged at 4,000 rpm/15 minutes at 4^{o}c to obtain platelet poor plasma (PPP). Screening was carried out by preparing a 1:1 mixture of patient plasma (with prolonged APTT) and normal pooled plasma (NPP) and incubating it for 1 and 2 hours. A second incubation of patient plasma and NPP was undertaken simultaneously for the same duration of time at 37^{o}C. APTT was performed on patient plasma with NPP taken as control, 1:1 mix control: patient incubated mix, and on 1:1 control: patient immediate mix (50:50 mix from normal plasma and patient plasma incubated separately) at 1 hour and 2 hours, with the results of APTT expressed in seconds. Those mix samples revealing more APTT prolongation of more than 10 seconds after incubation of 1 hour and 2 hours were considered inhibitor positive.

Samples found to be inhibitor positive after the screening assay were subjected to Bethesda assay, followed by the Nijmegen modification (in the case of low titre inhibitors) [14]. Patients were classified as having high titre or low titre inhibitors based on the results [15].

Results

An overview of results is shown in Table 1.

A total of 114 patients attending our HTC consented to participate in the study. Nineteen were excluded following the collection of samples as they showed bleeding disorders other than haemophilia A (including haemophilia B and von Willebrand disease).

Of the 95 study participants, 16 were aged up to 10 years (16.84%), 39 were aged 11–20 (41.05%), 32 were aged 21–30 (33.68%), 27 were aged 31–40 (7.37%), and one was aged over 40 (1.05%).

Seventeen participants had inhibitors (17.90%), out of which 4 patients were known to have inhibitors (4.21%). Within the respective age groupings, 4 (25%) of those aged up to 10 years had inhibitors, 7 of those aged 11-20 (17.95%), 5 of those aged 21-30 (15/63%), and 1 of those aged 31-40 (14.29%). Bethesda assay showed that of 17

PwHA with inhibitors, 5 (29.41%) had a high titre and 12 (70.58%) had a low titre.

In respect of disease severity, the majority of participants (45/95; 47.47%) had severe haemophilia A. Among the 17 participants with inhibitors, 9 (52.95%) had severe haemophilia A, 5 (29.41%) had moderate haemophilia A, and 3 (17.64%) had mild haemophilia A. Over one third of those with inhibitors had a known family history of inhibitors (6/17; 35.29%); 6 (7.69%) of the 78 participants without inhibitors had a known family history of inhibitors.

The incidence of inhibitor development was found to be higher in patients who were on recombinant factor replacement therapy (11/17; 64.70%) in comparison to plasma-derived factor replacement therapy (6/17; 35.30%). Among the patients with inhibitors, inhibitors developed after a median cumulative number of 17 exposure days.

The incidence of complications was found to be higher in participants who had developed inhibitors, with haemarthrosis and haematoma the most common. Haemarthrosis was reported by 76.47% (13/17) of those with inhibitors and 58.97% (46/78) of those without; haematomas were reported by 64.70% (11/17) of those with inhibitors and 38.46% (30/78) of those without. Only one PwHA among all study participants reported neurologic complications; this was a person with an inhibitor.

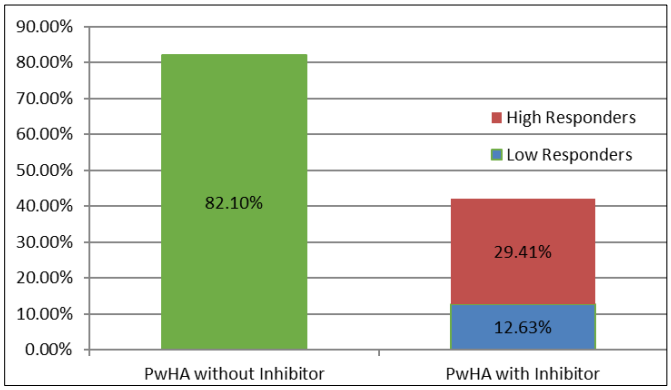

Fig 1: Showing incidence of inhibitor development in Haemophilia A.

Table 1: Overview of variables compared between PwHA with inhibitors and PwHA without inhibitors (N=95)

Variable	PwHA with inhibitors (N=17)	PwHA without inhibitors (N=78)
Age		
1-10	4(23.53%)	12(15.38%)
11-20	7(41.17%)	32(41.02%)
21-30	5(29.41%)	27(34.61%)
31-40	1(5.89%)	6(7.70%)
>40	0	1(1.29%)
Education status of parents		
Illiterate	6(35.29%)	14(17.94%)
School	5(25.41%)	32(41.03%)
High school	4(23.53%)	23(29.49%)
Graduate	2(11.77%)	9(11.54%)
Severity		
Mild	3(17.64%)	17(21.79%)
Moderate	5(29.41%)	25(32.05%)
Severe	9(52.95%)	36(46.16%)
Known family history of inhibitors	6(35.29%)	6(7.69%)
Age of starting factor replacement therapy		
< 10years	15(88.23%)	60(76.92%)
> 10 years	2(11.77%)	18(23.07%)
History of surgical procedure present	4(23.52%)	14(17.94%)
Type of factor product used		
Recombinant	11(64.70%)	48(61.53%)
Plasma-derived	6(35.30%)	30(38.47%)
Clinical manifestation		
Haemarthrosis	13 (76.47%)	46 (58.97%)
Haematoma	11 (64.70%)	30 (38.46%)
Gum bleeding	6 (35.29%)	32 (41.02%)
Haematuria	3 (17.64%)	4 (5.12%)
Neurologic complications	1 (5.88)	0 (0%)

Table 2: Age and severity wise distribution in PwHA with and without inhibitors.

Age Group	PwHA With Inhibitors	PwHA Without Inihibitors
<10 YEARS 4.2% (n=4) 12.6% (n=12)		
Mild	50% (n=2)	50% (n=6)
Moderate	50% (n=2)	30% (n=4)
Severe	0	20% (n=2)
11-20 years: 7.36% (n=7) 33.6% (n=32)		
Mild	14.2% (n=1)	25% (n=8)
Moderate	28.5% (n=2)	31.25% (n=10)
Severe	57.1% (n=4)	43.7% (n=14)
21-30 YEARS 5.2% (n=5) 28.42% (n=27)		

Mild	0%	25.9% (n=7)
Moderate	40% (n=2)	29.62% (n=8)
Severe	60% (n=3)	44.4% (n=12)
31-40 YEARS 1.05% (n=1) 6.31% (n=6)		
Mild	0%	33.3% (n=2)
Moderate	0%	33.3% (n=2)
Severe	100% (n=1)	33.3% (n=2)
>40 Years 0% 1.05% (n=1)		
Mild	0%	0%
Moderate	0%	0%
Severe	0%	100% (n=1)

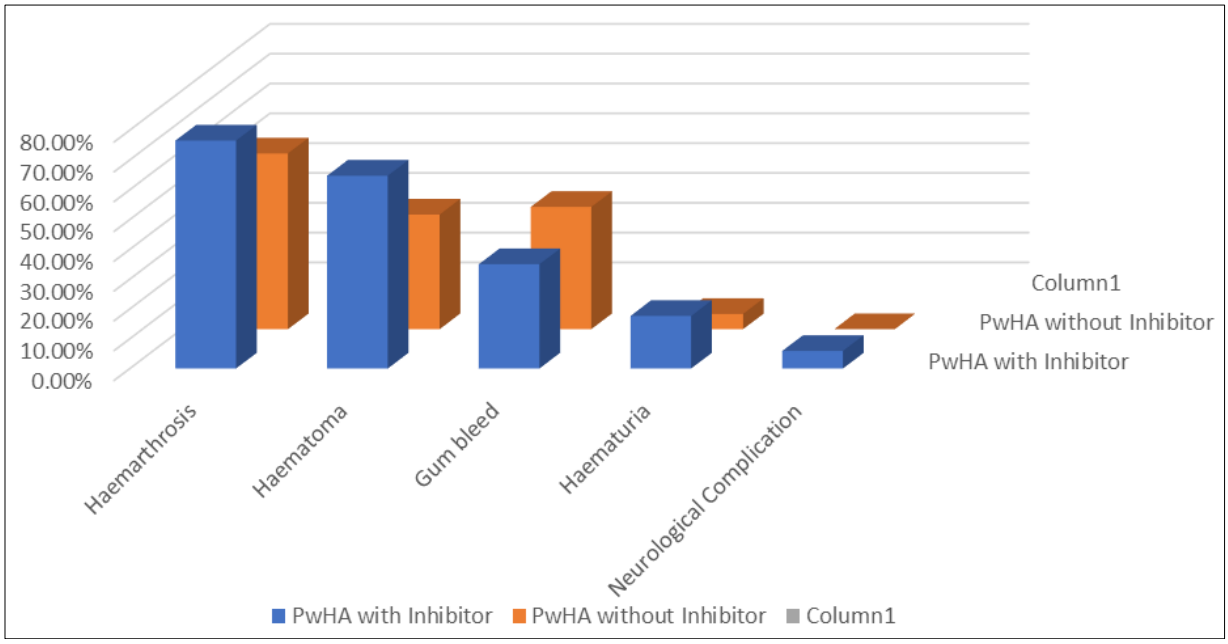

Fig 2: Complications in PwHA

Discussion

PwHA with inhibitors around the world experience impaired quality of life because of inadequate treatment response, leading to complications, disability and increased expenditure [8, 9, 16]. The purpose of our study was to estimate how the burden of inhibitors in PwHA correlates with clinical parameters, to gain a better insight into how we may be able to best manage PwHA with inhibitors at our HTC.

The incidence of alloantibodies against clotting factors varies geographically, as reflected in different studies. For example, the incidence of inhibitors among PwHA has been reported as being 13.04% in southern India and less than 8% in western India [17]. However, the cumulative incidence of inhibitors globally is estimated to be around 30% [11]. In this study, we found a prevalence of 17.90% among PwHA receiving treatment at our HTC. The prevalence has increased from the 5% reported in the study by Pinto *et al.* in 2014 [17], probably due to the smaller sample size in the latter (95 vs. 20) and increased rates of diagnosis.

The majority of our study population were aged 11–20 years (39/95; 41.17%), followed by 21–30 years (32/95; 33.68%). These groups represented 41.18% and 29.41% of PwHA with inhibitors respectively. Sixteen participants were aged under 10 years; the lower number of participants in this age range could be due to mild and moderate cases of haemophilia being less likely to be diagnosed at an early age [16]. 81.25% (n=13) patients under the age of 10 years had severe disease. This included 4 PwHA with inhibitors in this group, which represents 25% of the group. As already mentioned, majority of the PwHA in this group had severe disease and the prevalence of inhibitors is more among the severe patients, owing to their dependence on repeated factor replacement therapy. Also 2 patients needed high dose of factor replacement because of surgery post road traffic accident and fracture resulting in major thigh bleed(1). Far fewer PwHA with and without inhibitors were represented in the groups aged 31-40 and over 40 years. This could be due to limited access to treatment facilities, considering rural areas account for 81.73% of Northeast India, along with mortality due to blood borne infections such as AIDS, and hepatitis B and C [18,19].

In our study, of 78 PwHA without inhibitors, 36 (46.16%) had severe haemophilia A, 25 (32.05%) moderate, and 17 (21.79%) mild. Whereas, of 17 PwHA with inhibitors, 9 (52.95%) had severe haemophilia A, 5 (29.41%) moderate, and 3 (17.64%) mild. The proportion of severe diseases in both groups were quite high. This can be explained as patients with mild to moderate disease have fewer symptoms and, as a result, not having approached the hospital and hence potentially not having been diagnosed. Our study findings are similar to those found in a previous study of inhibitors in western India by Shah *et al.* [16](2,3)

In our study, 6 (35.29%) PwHA with inhibitors reported a positive family history of inhibitors in comparison to 6 (7.69%) PwHA without inhibitors. This The Malmö International Brother Study has previously shown PwH with a positive family history to have a 48% risk of inhibitor development in comparison to 15% in those with no family history [20]. The CANAL study, investigating treatment-related risk factors for developing inhibitors in previously

untreated PwHA also found a three-fold increased risk in patients with a positive family history of inhibitors compared with those with no family history [21].

Also similar to the results of the CANAL study, our study found that PwHA who developed inhibitors started factor replacement therapy at an earlier age in comparison to PwHA without inhibitors.(4) PwHA who were initiated on factor replacement therapy before the age of 10 years had more prevalence of inhibitor than the ones who were started later on (88.2% vs 11.77%).

Any major surgical procedure *has always been associated with increased exposure* to factor replacement therapy, both during and after the procedure, increasing the patient's susceptibility to inhibitor formation [21]. We had similar findings, findings, with 4 (23.52%) of the 17 PwHA with inhibitors having a history of surgical procedure.

It has been established in many studies that the incidence of inhibitor development is higher in people with severe haemophilia A compared to those with mild and moderate forms, with an average of 25-30% [16, 22-24]; however, incidence has been reported as high as 52% by Ehrenforth *et al*. [25]. In our study we reported a prevalence of 52.95% inhibitors in participants with severe haemophilia A, followed by 29.4% in moderate and 17.64% in mild cases. The titre of inhibitors is calculated by Bethesda assay, which classifies PwH with inhibitors as high and low responders, depending on the titre (>5 BU/mL and <5 BU/mL respectively), which further determines the course of treatment. High responders being more difficult to treat [26]. In our study, 12 out of 17 PwH with inhibitors were low responders and remaining were high responders. Our study also reported that the prevalence of inhibitors was higher among recipients of recombinant factor (64.70%) as compared with plasma-derived treatment (35.30%). Similar findings were reported in a study in France by Goudemand *et al*. [27], although other studies have shown that the incidence of inhibitor development did not vary with the type of product used for factor replacement [21, 28, 29]. An important point of difference, however, is that all of these studies were undertaken in well-resourced countries and were not representative of Indian ethnicity. Ethnicity has been shown to play a role in the formation of inhibitors in response to factor replacement among African-American and Latino haemophiliacs [30]; we are unaware of any studies that have confirmed this to be the case among PwH in India, but this is could be a factor that warrants further study.

Five complications associated with haemophilia were noted in our study: haemarthrosis, haematoma, gum bleeding, haematuria and neurologic complications. Haemarthrosis was the most common (76.47%) in PwHA with inhibitors, compared to (58.97%) in PwH A without inhibitors. The least common complication was intracranial haemorrhage, which was seen in one participant with inhibitor formation. These findings are similar to those reported by Gringeri *et al*. and Shah *et al*. [16, 31]. With the exception of gum bleeding, all other complications were reported more frequently in participants with inhibitors.

As a developing nation, India is still facing the challenge of providing basic factor replacement therapy to haemophilia patients, and the north-eastern part of the country is even more poorly resourced compared to some other parts of the country. However, there is a steady rise in awareness of haemophilia among the general population which has led to more diagnosis and more utilisation of the treatment facilities that are available, thanks to the work of government agencies and WFH. As more PwH are treated with factor replacement, it is perhaps inevitable that we will also see a rise in the number of PwH with inhibitors and the associated burden in terms of cost, morbidity and quality of life.

Conclusion

With all the data, we concluded that, prevalence of inhibitor was more in severe forms of the disease, complications were more in PwHA with inhibitors and recipients of recombinant product were more likely to have inhibitors.

Our study showed that 17.89% (n=17) PwHA developed inhibitors, which was more in age group, severity and after surgical procedures. This emphasizes the need for regular factor assessment and inhibitor screening as 1/5th of our patients developed inhibitor of which majority patients have low titre at our treatment centre.

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