FREQUENCY OF INHIBITORS AMONG KNOWN HAEMOPHILIA -A PATIENTS

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Abstract

Background: Inhibitors are IgG alloantibodies which are directed against exogenous clotting factor VIII that neutralize the function of infused clotting factor concentrate used for the treatment. The prevalence of inhibitors in Hemophilia A is around 30% worldwide. Inhibitors occur as a result of natural immune process of the body as factor concentrates used for treatment are foreign to the body and patient's own body either produces no factor or produces structurally abnormal protein. The objective of this study is to determine the frequency of inhibitors among known hemophilia A patients.

Methods: Cross-sectional survey done including 100 male patients of hemophilia A and on treatment for more than 1 year, from 2 to 60 years of age. All the patients were undergone aPTT based screening for inhibitor, both immediately and two hours after mixing the patients plasma with the normal plasma.

Results: Age range in this study was from 2 to 60 years with mean age of 37.21 ± 14.73 years. Frequency of inhibitors among known hemophilia A patients was 18 (18.0%) of cases.

Conclusion: Frequency of inhibitors among known hemophilia A patients is considerably high.

Keywords: Hemophilia A, inhibitors, severity.

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Hemophilia is an X-linked bleeding disorder which is due to deficiency of factor VIII or factor IX in the plasma resulting in hemophilia A or hemophilia B respectively.[1] It is due to defect in F8 and F9 genes respectively which play essential role in intrinsic pathway of the coagulation cascade resulting in defective clot formation.[2] Prevalence of hemophilia A is 1 in 5000 males and that of hemophilia B is 1 in 35000 males worldwide which clearly shows that hemophilia A is more common than hemophilia B.[3]

Hemophilia A classification according to plasma procoagulant levels is as follows: Severe hemophilia - FVIII level less than 1% of normal (< 0.01 IU/mL),

Moderate hemophilia - FVIII level 1-5% of normal (0.01-0.05 IU/mL). Mild hemophilia - FVIII level more than 5% up to 45% of normal (>0.05 to < 0.45 IU/mL).

Severe disease presents in children younger than 1 year and accounts for 43-70% of hemophilia A cases. Moderate disease presents in children aged 1-2 years and accounts for 15-26% of cases. Mild disease presents in children older than 2 years and accounts for 15-31% of cases.[3,4]

In terms of the symptoms of hemophilia A, there are internal or external bleeding episodes. Individuals with more severe hemophilia suffer more severe and more frequent bleeding, while others with mild hemophilia typically suffer more minor symptoms except after surgery or serious trauma. Moderate hemophiliacs have variable symptoms which manifest along a spectrum between severe and mild forms.[2] The treatment of hemophilia involve management of bleeding episodes, prophylaxis, immune tolerance induction for patients with factor inhibitors, and treatment and rehabilitation of patients with hemophilia synovitis. Treatment of patients with hemophilia ideally should be provided

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through a comprehensive hemophilia care center. Major complication associated with treatment of hemophilia is the formation of inhibitors[3]. Inhibitors are the neutralizing or allo-antibodies which are directed against factor concentrates used for the treatment. The prevalence of inhibitors in Hemophilia A is around 30% worldwide[5]. Risk factors for inhibitor formation includes genetic factors i.e positive family history, underlying mutation, race or immune factors and non-genetic factors i.e type of treatment products, age at first exposure to treatment, duration and intensity of treatment.[6,7] Previously untreated patients are at greatest risk for inhibitor formation.[8] Inhibitors are associated with increased mortality and morbidity. The rationale of this study was to determine frequency of inhibitors in known hemophilia A patients presenting to Hematology department of tertiary care hospital. However, the existing literature of Asia shows considerable variation in frequency ranging from 20.57% to 29.3% in hemophilia A. Thus, this study will give insight to the clinicians regarding the magnitude of inhibitors in hemophilia A in Pakistan and to develop screening guidelines in these patients for early diagnosis and management of patients with inhibitors. This study will also provide baseline data on which further research can be conducted regarding risk factors of inhibitors to decrease mortality and morbidity in hemophiliac patients.

METHODS

Cross-sectional survey was conducted at Haematology department, Lahore General Hospital, Lahore from January 2022-July 2022. Non-probability, consecutive sampling done. About 100 known hemophilia A patients fulfilling the inclusion criteria were approached and an informed consent was taken from them before enro-lling in the study. Information regarding their demo-graphic data was noted in the proforma. All the patients were undergone aPTT based screening for inhibitor, both immediately and two hours after mixing the patients plasma with the normal plasma. Confidentiality of the data was ensured. Inhibitors were labeled as per-opera-tional definition.

Inclusion Criteria:

- Age 2-60 years
- Patients on treatment for more than 1 year.

Exclusion Criteria:

- Patients with history of inhibitors previously.
- Patients taking anti-thrombotic drugs.
- Patients with liver disease.
- Patients with vitamin K deficiency.

Data was entered and analyzed using SPSS version 20.0. Numerical variable i.e. age was summarized as mean and standard deviation. Qualitative variables i.e. presence of inhibitors were presented in the form of frequency and percentages. Data was stratified for age, gender, age at first treatment and duration of treatment. Chi-square test was applied to check statistical significance with 'p' value <0.05 as statistically significant.

RESULTS

Age range in this study was from 2 to 60 years with mean age of 30.63 ± 14.71 years. 56% were between 2-30 years age group and 44% were in 31-60 years age group. Mean duration of treatment was 5.56 ± 1.07 years (Table I). Frequency of inhibitors among known hemophilia A patients was seen in 18 (18.0%) of cases.

Stratification of inhibitors with respect to age groups is shown in Table 2. Table 3&4 have shown the stratification of inhibitors with respect to duration of treatment and inhibitors with respect to age at first treatment

Table 1: *Distribution of patients according to duration of treatment.*

Duration of treatment (years)	Total (n=100)	
	No. of patients	%
≤5 years	51	51.0
>5 years	49	49.0
Mean ± SD	**5.56 ± 1.07 years**	

Table 2: *Stratification of inhibitors with respect to age groups.*

Age (years)	inhibitors		p-value
	Positive	Negative	
2-30	12 (21.43%)	44 (78.57%)	**0.314**
31-60	06 (13.64%)	38 (86.36%)	

Table 3: Stratification of inhibitors with respect to duration of treatment.

Duration of disease (years)	inhibitors		p-value
	Positive	Negative	
≤5	08 (15.69%)	43 (84.31%)	**0.539**
>5	10 (20.41%)	39 (79.59%)	

Table 4: Stratification of inhibitors with respect to age at first treatment.

Age at first treatment (years)	inhibitors		p-value
	Positive	Negative	
≤30	07 (11.67%)	53 (88.33%)	**0.044**
>30	11 (27.50%)	29 (72.50%)	

DISCUSSION

This study has been conducted to determine the frequency of inhibitors among known hemophilia A patients. Age range in this study was from 2 to 60 years with mean age of 37.21 ± 14.73 years. Frequency of inhibitors among known hemophilia A patients was seen in 18 (18.0%) of cases. Patel et al reported a frequency of inhibitors in hemophilia A patients as 20.57%[1] and Owaidah et al reported a slightly higher frequency as 29.3%.[3] Soucie et al. study showed that total 2156 patients had HA. Of those with available F VIII measurements, 1140 (43%) had severe (F VIII <1%), 684 (26%) had moderate (F VIII 1%–5%), and 848 (31%) had mild (F VIII 6%–30%) disease.[9]

However, there are few studies regarding the prevalence of hemophilia inhibitors among Arab patients. In an Egyptian study, inhibitors were detected in 18.2% of the patients with hemophilia A and in 9.1% of the patients with hemophilia B, and although mild-to-moderate hemophilia was more common than severe hemophilia, inhibitors were more common in patients with severe hemophilia.[10] In a Tunisian study, the prevalence of FVIII and FIX inhibitors was much lower (5%).[11] The incidence of inhibitor formation varies according to ethnicity, with higher rates observed among African-American, Latino, and Hispanic patients.[12] Western studies typically report a relatively low incidence of clinically significant long-term inhibitors (approximately 10%), although higher rates have been observed when both transient and persistent inhibitors are considered.

In a Japanese study, 26.8% of patients with hemophilia A developed inhibitors, although 70.7% of these patients lost their inhibitors by the end of the 2-year study period.[13,14] A study in Pakistan, found inhibitors in only 15% of 140 patients with hemophilia A; these patients exhibited various degrees of severity and different replacement treatments (FVIII concentrate, fresh frozen plasma, or cryoprecipitate).[15] Nevertheless, these discrepancies may be related to differences in the study populations, management trends, and testing strategies.

A study of 102 Iranian patients with hemophilia A (44 severe cases, 28 intermediate cases, and 30 mild cases) found that only 20 patients (19.6%) had inhibitors (11 severe cases, 5 intermediate cases, and 4 mild cases)[16]. A large Indian study of 1285 patients with hemophilia A found that only 6.07% of the patients had inhibitors, although there were remarkable regional variations (the highest prevalence was 20.99%).[17] We also found a higher prevalence of inhibitors among patients who were receiving recombinant factors, and this result agrees with the findings from previous studies.[18,19]

Inhibitors are most commonly encountered in people with severe hemophilia A (overall 25-40% lifetime risk) compared to those with moderate/mild hemophilia A (overall 5-15% lifetime risk). In patients with severe hemophilia (A or B), the risk of inhibitor development is highest during the first 20 exposures to factor replacement after which the risk decreases dramatically, particularly from 20 Exposure Days (ED) to 50 ED. After 50 ED the risk, although already quite low, decreases further reaching a very low steady-state rate of 2-5 per 1,000 patients per year by 150 ED.[20,21] Therefore, having reached a minimum of 150 ED has been the classical definition of a patient referred to as a previously treated patient (PTP). In the Research of Determinants of Inhibitor Development (RODIN) study, the largest study of previously untreated patients (PUP) with severe hemophilia A (n>600 patients), inhibitors developed after a median of 15 ED.[22]

CONCLUSION

Frequency of inhibitors among known hemophilia A patients is quite high. So, we recommend that early detection and management of inhibitors should be done in these particular patients in order to reduce the mortality and morbidity of community.

Conflict of Interest *None*

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REFERENCES

1. Patel T, Shah S, Bhatnagar N, Gajjar M, Shah M, Tripathi S. "Prevalence of Inhibitors in Hemophilia Patients and its Clinical Implications": A Study of 276 Patients in Western India. Global Journal of Transfusion Medicine. 2019Oct17; 4(2):168–74.
2. Marlar RA, Strandberg K, Shima M, Adcock DM. Clinical utility and impact of the use of the chromogenic vs one-stage factor activity assays in haemophilia A and B. European Journal of Haematology. 2019; 104 (1): 3–14.
3. Owaidah T, Momen AA, Alzahrani H, Almusa A, Alkasim F, Tarawah A, et al. The prevalence of factor VIII and IX inhibitors among Saudi patients with hemophilia. Medicine. 2017;96(2):1–7.
4. Giangrande PLF, Hermans C, O'Mahony B, Kleijn PD, Bedford M, Batorova A, et al. European principles of inhibitor management in patients with haemophilia. Orphanet Journal of Rare Diseases. 2018Apr27; 13(1): 1–6.
5. Kim JY, You CW. The prevalence and risk factors of inhibitor development of FVIII in previously treated patients with hemophilia A. Blood Research. 2019 Sep; 54(3):204–9.
6. Miller CH. Laboratory testing for factor VIII and IX inhibitors in haemophilia: A review. Haemophilia. 2018; 24(2):186–97.
7. Nazir HF, Khanbashi LA, Wali YA. Screening for inhibitor development and its risk factors in patients with severe haemophilia A in Oman. Hematology & Transfusion International Journal. 2018May16; 6(3).
8. Peyvandi F, Garagiola I. Product type and other environmental risk factors for inhibitor development in severe hemophilia A. Research and Practice in Thrombosis and Haemostasis. 2018 Apr 18; 2(2):220–7.
9. Soucie JM, Evatt B, Jackson D. Occurrence of hemophilia in the United States. The hemophilia surveillance system project investigators. Am J Hematol 1998; 59:288-94.
10. Abdelrazik N, Rashad H, Selim T, et al Coagulation disorders and inhibitors of coagulation in children from Mansoura, Egypt. Hematology 2007; 12: 309–14.
11. Kraiem I, Hadhri S, El Omri H, et al Frequency of specific coagulation inhibitors and antiphospholipid antibodies in Tunisian haemophiliacs. Ann Biol Clin (Paris) 2012; 70:659–65.
12. Carpenter SL, Michael Soucie J, Sterner S, et al Hemophilia Treatment Center Network (HTCN) Investigators Increased prevalence of inhibitors in Hispanic patients with severe haemophilia A enrolled in the Universal Data Collection database. Haemophilia 2012; 18:e260–5.
13. Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. Haemophilia 2003; 9:418–35.
14. Shirahata A, Fukutake K, Higasa S, et al An analysis of factors affecting the incidence of inhibitor formation in patients with congenital haemophilia in Japan. Haemophilia 2011; 17:771–6.
15. Borhany M, Kumari M, Shamsi T, et al Frequency of factor VIII (FVIII) inhibitor in haemophilia A. J Coll Physicians Surg Pak 2012;22:289–93.
16. Modaresi AR, Torghabeh HM, Pourfathollah AA, et al Pattern of factor VIII inhibitors in patients with hemophilia A in the north east of Iran. Hematology 2006; 11:215–7.
17. Pinto P, Shelar T, Nawadkar V, et al The epidemiology of FVIII inhibitors in Indian haemophilia A patients. Indian J Hematol Blood Transfus 2014; 30:356–63.
18. Lusher JM. Is the incidence and prevalence of inhibitors greater with recombinant products? No. J Thromb Haemost 2004; 2:863–5.
19. Goudemand J, Laurian Y, Calvez T. Risk of inhibitors in haemophilia and the type of factor replacement. Curr Opin Hematol 2006; 13:316–22.
20. Peerlinck K, Hermans C. Epidemiology of inhibitor formation with recombinant factor VIII replacement therapy. Haemophilia 2006; 12:579–90.
21. Fischer K, Lassila R, Peyvandi F, Calizzani G, Gatt A, Lambert T et al. Inhibitor development in haemophilia according to concentrate. Four-year results from the European Haemophilia Safety Surveillance (EUHASS) project. Thrombosis and Haemostasis, 2015; 113 (5): 968-75.
22. Gouw SC, van der Bom JG, Ljung R, Escuriola C, Cid AR, Claeyssens-Donadel S et al. Factor VIII products and inhibitor development in severe hemophilia A. New England Journal of Medicine, 2013; 368(3): 231-9.