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ORIGINAL ARTICLE

The Survey of Effective Agents on Factor VIII and IX Inhibitors in Patients with Hemophilia A and B in Kermanshah Province

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ABSTRACT

Background: Hemophilia is the most frequent severe hereditary hemorrhagic disease due to deficiency of coagulation factors VIII (Hemophilia A) or IX (Hemophilia B) in plasma. We aimed to identify patients with hemophilia in Kermanshah, Iran and assess the incidence of inhibitors in this population and its associated factors.

Methods: This study was conducted on patients with hemophilia A and B admitted in hospitals of Kermanshah city, referred to coagulation laboratory of Kermanshah blood transfusion organization. Variables including age, sex, family history of the patients in terms of history of hemophilia and inhibitor formation, development of inhibitor in patients, age at starting the treatment, blood group, severity of hemophilia, average of factors received per month and liver disease were assessed in patients.

Results: Of 123 patients with hemophilia A, 119 (96.7%) were men. The mean±SD age of patients with hemophilia A was 25.9±15.74 years. Only five men had developed factor VIII inhibitor. Of 25 patients with hemophilia B, 24 (96%) were men with a mean±SD age of 21.7±15.71 years. Factor IX inhibitor was not detected in any patient. There was no association between incidence of inhibitors and age at the onset of the treatment, family history of hemophilia, blood group, severity of hemophilia, average of received factor per month and liver disease. However, a positive association between incidence of inhibitors and family history of inhibitors was found (P<0.05).

Conclusion: Association between family history of inhibitor and incidence of inhibitor formation in hemophilic patients was a new finding. Therefore this outcome and genetic evaluation of these for finding relevant mutations should be considered.

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Introduction

Hemophilia is the most frequent hereditary hemorrhagic disease. Hemophilia A is the most common congenital severe bleeding disorder and is the result of a deficiency in the clotting protein factor VIII.[1,2] Factor VIII (FVIII) deficiency is an X-linked recessive disorder occurring in 1 in every 5000 male births without an ethnic predominance [3], but hemophilia B is prevalent in one in every 30000 male births.[4] According to the global survey carried out by World Federation of Hemophilia, Iran was ranked as the second in the eastern Mediterranean region next to Egypt; however, the size and distribution of the Iran hemophilic population is not well known.[5] Understanding the pathophysiological mechanisms leading to the development of inhibitory anti factor VIII antibodies in patients with hemophilia A has improved considerably over the last 2 decades.[6] In patients who have developed high titers of antibodies (inhibitors) against factor concentrates, acute bleeding can be inhibited by administering bypass agents, but it is difficult to predict

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the effectiveness of such treatment in individual cases.[7] Different attempts have been suggested to overcome or eradicate against development of coagulation factor inhibitors. Immune tolerance induction (ITI) is an effective strategy often warranted in these patients.[8] A variety of mutations in the genes encoding FVIII or FIX on X chromosome is being defined that lead to non-functional proteins or their complete absence. Generally, point mutations in the F9 gene can lead to severe hemophilia B, whereas deletions or major inversions in the F8 gene lead to severe hemophilia A.[9] In Iran, most patients with hemophilia A have received several replacement therapies such as fresh frozen plasma (FFP), cryoprecipitate, and factor VIII concentrate. We aimed to determine the number of patients with inhibitor and associated factors in a population of patients with hemophilia referring to Kermanshah blood transfusion organization.

Patients and Methods

In this descriptive cross-sectional study, all patients with hemophilia referred to coagulation laboratory of Kermanshah blood transfusion organization were enrolled. Two ml blood with 9 to 1 ratio with 3.2 grams per deciliter of sodium citrate was obtained and centrifuged with speed of 2000/15 RPM for preparing of *platelet poor plasma*. Then, 0.2 ml plasma was combined with 0.2 ml of normal plasma (at least 15 samples of healthy individuals) and control sample was contained 0.2 ml normal plasma with 0.2 ml deficient factor *VIII* for hemophilia type A and 0.2 ml normal plasma with 0.2 ml deficient factor IX for hemophilia type B. Samples were kept for 2 to 4 hours to measure factor *VIII* inhibitor and 1 hour for factor IX inhibitor in a water bath at 37 °C. After this period, factor *VIII* and IX were measured with Coagulometer STAGO using a formula based on the level of coagulation factor inhibitor in Bethesda unit. Data were analyzed using descriptive statistics and analysis of T-test, Chi-square test and *Mann-Whitney U* non-parametric test with SPSS 19.

Table 1: The characteristics for hemophilia A (n=123)

Variables	n(%)	Mean±SD
Age(year)		25.9±15.7
Sex		
Male	119(71.1)	
Female	4(28.9)	
Marital Status		
Single	69(56.4)	
Married	54(43.7)	
Education Status		
Illiterate	18(14.6)	
Less than diploma	76(61.8)	
Diploma	15(12.2)	
College education	14(11.4)	
The Distribution		
Kermanshah	61(49.6)	
Songor	12(9.8)	
Other cities	50(40.6)	
Kind of Blood Type		
O^+	47(38.2)	
A^+	45(36.6)	
Other	31(25.2)	
Separation of Intensity Disease		
Mild	19(15.4)	
Moderate	30(24.4)	
Severe	74(60.2)	
Hepatic Involvement		
Positive	65(52.8)	
Negative	58(47.2)	
Treatment Start's Age(month)		
<6	18(14.6)	
6-12	25(20.3)	
>12	80(65.1)	
Family History of Hemophilia A		
Positive	75(60.1)	
Negative	48(39.9)	
Family History of Inhibitor		
Positive	5(4.9)	
Negative	118(95.1)	

Results

Out of 148 patients with hemophilia, 123 had hemophilia A and 25 had hemophilia B. Of the 123 patients with hemophilia A, 119 (96.7%) were men. The mean±SD age of the patients was 25.9±15.74 years. There were only five men with FVIII inhibitor. Female patients did not develop any FVIII inhibitor. Sixty-nine patients (56.4%) patients were single and 54(43.7%) were married. Eighteen patients (14.6%) were illiterate, 76(61.8%) were less than high school diploma, 15(12.2%) had diploma certificate and 14(11.4%) had college education. Majority of patients (49.6%) with hemophilia A were from Kermanshah city and then Songor city (9.8%). Frequency of blood groups O+ and A+ in the patients was 38.2% and 36.6%, respectively (Table 1).

Out of 25 patients with hemophilia B, 24 (96%) were men with a mean±SD age of 21.7±15.71 years. No patient developed factor IX inhibitor. Twelve patients (48%) patients were single and 13(52%) were married. Two patients (8%) were illiterate, 11(44%) were less than high school diploma, 5(20%) had diploma certificate and 7(28%) had college education. Majority of patients (60%) with hemophilia B were from Kermanshah province (Iran). Frequency of blood groups O+ and A+ in the patients was 56% and 20%, respectively (Table 2).

There was no association between incidence of inhibitors and age at onset of treatment, family history of hemophilia, blood group, severity of hemophilia, average of factors received per month and liver disease. But we found an association between development of inhibitors and family history of inhibitor formation ($P<0.05$).

Discussion

Incidence of development of inhibitors in patients with hemophilia A in different studies have been reported to be from 8.5-27%.[10-16] In our study it was 4% and all patients were men. In a study reporting hemophilia from Iran, neither of patients with hemophilia B developed inhibitor similar to our study.[10] The most and least common blood groups in our patients with inhibitor

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Table 2: The characteristics for hemophilia B (n=25)

Variables	n(%)	Mean±SD
Age(year)		21.7±15.7
Sex		
Male	24(96)	
Female	1(4)	
Marital Status		
Single	13(52)	
Married	12(48)	
Education Status		
Illiterate	2(8)	
Less than diploma	11(44)	
Diploma	5(20)	
College education	7(28)	
Kind of Blood Type		
O^+	14(56)	
A^+	5(20)	
Other	6(24)	
Separation of Intensity Disease		
Mild	7(28)	
Moderate	8(32)	
Severe	10(40)	
Hepatic Involvement		
Positive	11(44)	
Negative	14(66)	
Treatment Start's Age (month)		
<6	4(16)	
6-12	4(16)	
>12	18(68)	
Family History of Hemophilia B		
Positive	22(88)	
Negative	3(12)	
Family History of Inhibitor		
Positive	0(0)	
Negative	25(100)	

were O and AB blood groups, respectively, compatible with blood group frequency in the general population.[17] Most of our patients with hemophilia A and B had blood groups O^+ and A^+. The patient's age is generally accepted to be an important risk factor for inhibitor development.[18] There are conflicting data regarding age at first treatment as a risk factor for inhibitor formation. Two small cohort studies found an inverse association between the age (<6 months) of first exposure to factor and inhibitor formation but they were not controlled for other risk factors for inhibitor formation.[19,20] We found no association between incidence of inhibitors and age at which treatment was started. Inhibitor formation was a less common complication in patients with mild or moderate hemophilia occurring in approximately 3–13% of them.[15,21] In a comprehensive study from Iran it was indicated that there was a significant association between disease severity and inhibitor formation (P<0.0001).[10] Another study showed that overall prevalence of inhibitor formation was 14.4%, whereas its prevalence in severe hemophilia A patients was reported to be 22.8%.[14] Inhibitor activity was not detected in either of the 14 patients with mild hemophilia while it was present in 9 of 27 (33%) patients with moderate, and 7 of 17 (41%) with severe disease.[16] Incidence of Inhibitor formation in mild and moderate hemophilia was 3.5% and 9.4%, respectively. Overall, 93% of the patients with inhibitor were of patients with moderate and severe hemophilia A.[22] In a study on 1280 patients, there were 368 (28.8%), 277 (21.6%) and 635 (49.6%) patients with mild, moderate and severe hemophilia A, respectively.[13] Of 123 patients with hemophilia A in this study, 19 (15.4%), 30 (24.4%) and 74(60.2%) had mild, moderate and severe type of the disease, respectively. Patients of African or Hispanic heritage have an increased risk of inhibitor formation.[23] We could not find any association between incidence of inhibitor with family history of hemophilia in the literature but such an association between inhibitor formation and family history of inhibitor did exist in our patients, although there was a very small population of only five and needs further studies confirming this finding (P<0.05).

Conclusion

Association between family history of inhibitors and incidence of inhibitor formation was a new finding in our study. Future studies including a large number of patients are required to approve such association and then look for more genetic mutations predisposing to development of inhibitors in hemophiliac patients.

Conflict of Interest: None declared.

References

1. Bauduer F, Degioanni A, Ducout L, Scribans C, Dutour O. Distribution of haemophilia in the French Basque country. Haemophilia. 2002;8(6):735-9.
2. Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. Lancet. 2003;361(9371):1801-9.
3. Soucie JM, Evatt B, Jackson D. Occurrence of hemophilia in the United States. The Hemophilia Surveillance System Project Investigators. Am J Hematol. 1998;59(4):288-94.
4. Evatt BL. Demographics of hemophilia in developing countries. Semin Thromb Hemost. 2005;31(5):489-94.
5. O'Mahony B.Global Haemophilia Care Challenge and Opportunities. Montreal, Canada: World Federation of Haemophilia, 2002. Available at: http://www.wfh.org (last accessed on 20 August 2008).
6. Astermark J. FVIII inhibitors: pathogenesis and avoidance. Blood. 2015;125(13): 2045-51.
7. Swedish Council on Health Technology Assessment. Treatment of Hemophilia A and B and von Willebrand disease: A Systematic Review [Internet]. Stockholm: Swedish Council on Health Technology Assessment (SBU); 2011 May. SBU Yellow Report No. 208E.
8. Astermark J, Santagostino E, Keith Hoots W. Clinical issues in inhibitors. Haemophilia. 2010;16 Suppl 5:54-60.
9. Scott DW. Inhibitors - cellular aspects and novel approaches for tolerance. Haemophilia. 2014;20 Suppl 4:80-6.

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10. Mehdizadeh M, Kardoost M, Zamani G, Baghaeepour MR, Sadeghian K, Pourhoseingholi MA. Occurrence of haemophilia in Iran. Haemophilia. 2009;15(1):348-51.
11. Schoppmann A, Waytes AT. Factor VIII inhibitor and severity of hemophilia. Thromb Haemost. 1996;76(2):280-1.
12. Kasper CK, Aledort L, Aronson D, Counts R, Edson JR, van Eys J, et al. Proceedings: A more uniform measurement of factor VIII inhibitors. Thromb Diath Haemorrh. 1975;34(2):612.
13. Sharifian R, Hoseini M, Safai R, Tugeh Gh, Ehsani AH, Lak M, et al. Prevalence of inhibitors in a population of 1280 hemophilia a patients in Iran. Acta Medica Iranica 2003;41(1): 66-8.
14. Ehrenforth S, Kreuz W, Scharrer I, Linde R, Funk M, Güngör T, et al. Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. Lancet. 1992;339(8793):594-8.
15. Sultan Y. Prevalence of inhibitors in a population of 3435 hemophilia patients in France. French Hemophilia Study Group. Thromb Haemost. 1992;67(6):600-2.
16. Oren H, Yaprak I, Irken G. Factor VIII inhibitors in patients with hemophilia A. Acta Haematol. 1999;102(1):42-6.
17. Goldman, Bernett. Cecil textbook of medicine. 2000; 2:1004-7.
18. Kavakli K, Gringeri A, Bader R, Nisli G, Polat A, Aydinok Y. Inhibitor development and substitution therapy in a developing country: Turkey. Haemophilia. 1998;4(2):104-8.
19. Lorenzo JI, López A, Altisent C, Aznar JA. Incidence of factor VIII inhibitors in severe haemophilia: the importance of patient age. Br J Haematol. 2001;113(3):600-3.
20. van der Bom JG, Mauser-Bunschoten EP, Fischer K, van den Berg HM. Age at first treatment and immune tolerance to factor VIII in severe hemophilia. Thromb Haemost. 2003;89(3):475-9.
21. Addiego J, Kasper C, Abildgaard C, Hilgartner M, Lusher J, Glader B, et al. Frequency of inhibitor development in haemophiliacs treated with low-purity factor VIII. Lancet. 1993;342(8869):462-4.
22. Colman RW, Hirsh J, Marden VJ, et al. Hemostasis & thrombosis, Basic principle & clinical practice. Fourth edition 2000; 1003-6.
23. Carpenter SL, Michael Soucie J, Sterner S, Presley R. Increased prevalence of inhibitors in Hispanic patients with severe haemophilia A enrolled in the Universal Data Collection database. Haemophilia. 2012;18(3):e260-5.

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