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Mini Review

Frequency of Factor VIII Inhibitors in a Developing Country; Iran Experiences

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Abstract

Hemophilia A, or classic hemophilia, is an X-linked recessive disorder of coagulation system that usually affects males. It mostly inherits from parents, while about 30% of individuals with hemophilia A inherit it via spontaneous mutations in factor VIII gene.

The mainstone of treatment in hemophilia A is replacement therapy with factor VIII concentrates. The major burden appeared in current decade in hemophilia was development of factor VIII inhibitors, that made challenges for both the patients and hematologists.

The factor VIII inhibitors have been paid suitably in developed countries. It seems that factor VIII inhibitors in developing countries need more attention to be paid. Here a review on published data on frequency of factor VIII inhibitors in diverse territories of Iran has been presented.

Keywords: Hemophilia; Factor VIII inhibitor; Frequency; Iran

Abbreviation

HA: Hemophilia A; FVIII: Factor VIII

Introduction

Hemophilia A (HA) is the most prevalent inherited coagulation factor with prevalence of 1: 5000-10 000 male birth in population. It inherited as X-linked recessive coagulation disorder [1,2]. The affected individuals have lower level of coagulation FVIII in plasma that terminated to bleeding manifestations in accidents, after trauma or spontaneously according to severity of disorder. The severity of disorder (severe, moderate, mild) is reflecting plasma level of FVIII in circulation (<1%, 1-5%, 5%>30%) respectively. The main stone of treatment of the affected individuals is replacement therapy with coagulation FVIII concentrates [3]. There are two main approaches for replacement therapy in hemophilia, inter alia, the first is on demand regimen, in this approach after happening bleeding episode **and** replacement therapy is giving to stop bleeding. This is more common therapy in mild type of hemophilia. The second is prophylaxis regimen that is used in moderate and severe forms and replacement therapy is administrated to prevent bleeding episodes [3,4].

Factor VIII (FVIII) is the largest multi-domains protein in coagulation system. It is targeted most commonly by immune system [5-7]. The factor VIII domains are indeed binding sites for various partner of FVIII in circulation and coagulation system, inter alia, von Willebrand factor, coagulation factor IX, lipid membranes, activate protein C and endocytic receptors [8-10]. There are genetical and none-genetical factors that facilitate development of FVIII inhibitors [11].

The FVIII inhibitors are mostly IgG antibodies against FVIII that bind to each other and make immune complexes [12]. These inhibitors hamper abilities of FVIII to do its roles in intrinsic pathway, hence causing continuity of bleeding despite infusion of coagulation FVIII concentrates in a patient with hemophilia and active bleeding. The FVIII inhibitors cause problems for both patients and hematologists who visiting bleeding patients [13]. The control of bleeding episodes in the individuals with inhibitor may be more complicated and more expensive than in individuals with hemophilia, but without inhibitor. It constrains financial charges and major problems for health providers systems. Also our experience on 102 patients with HA revealed that inhibitors can be developed in patients who are using various types of treatment including coagulation factor VIII, **concentrates** fresh frozen plasma, cryoprecipitate or mixture of them [14]. Forasmuch as it has importance in life of individuals with hemophilia, nowadays it accounts one of the most important issues in treatment of individuals with HA.

Having knowledge about prevalence and frequency of FVIII inhibitors in any region may be beneficial for health care provider and health policy makers. Owing to there is limited data on frequency of inhibitor antibodies of FVIII in HA in Iran, a country with more than 75 000 000 population and noticeable number of the patients with HA [1], here a review on published literatures is presented here.

Strategy of literatures review

The review of literatures was done using following key words: "He(a)mophilia + Iran + factor VIII inhibitor", "He(a)mophilia + Iran + inhibitor", "He(a)mophilia + Iran + factor VIII antibody" in PubMed and Scopus medical search engines without any time and language limitations. As well, not to miss any published contributions in this area, another literature reviews were done in Persian medical search engines; www.sid.ir & www.barakatkns.com with Persian versions of above key words without any limitation in time.

Results

After completing literature review, 103 articles revised and

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Table 1: A summary of published articles on frequency of factor VIII inhibitors in various parts of Iran until Feb 2015.

province	Year of publication	Mean age of patients	Type of treatment	No of patients with HA	Inhibitor (%)	Detection method of inhibitor	Low titer inhibitor	High titer inhibitor
Sanandaj [15]	2010	23.8±9.3	N	104	20 (19.2%)	Bethesda	16	4
Khorasan [14]	2006	24.8±14.7	Mix	102	20 (19.6)	Bethesda	N	N
Fras [16]	2011	N	N	56	8 (14.3%)	N	N	N
Mazandaran [17]	2013	22.23±1.99	Mix	52	9 (17.3%)	Bethesda	3	6
Tehran [18]	2003	N	N	1280	184 (14.4%)	Nijmegen	143	41
Total				1594	241 (15.11%)		162 (10.1%)	51 (3.2%)

Ref: reference; HA: hemophilia A; N: not cited; Mix: various type of coagulation concentrates have been used.

5 relevant papers that had been paid to determination of FVIII inhibitor in any part of Iran were selected and their full texts were retrieved [14-17].

Owing to Iran is a widespread country with 34 provinces and about 75 000 000 population, it is expected to have noticeable number of individuals with bleeding disorders. According to our ancient survey, there are about 8000 cases with bleeding disorders in Iran, individuals with HA comprises main part of them [1]. As the Figure 1 showed there are limited surveys on frequency of FVIII inhibitors in various part of the country despite huge number of the affected the patients. Merely we could find only 5 surveys that have been paid to this field (Table 1). These surveys had been done in provinces comprises: Khoarasan (in north-western part of country), Tehran (in middle part of the country), Fars (in south part of the country), Kurdestan (in west part of the country) and Mazandaran (in north part of the country). The total number of reported individuals with HA who examined for FVIII inhibitors included 1594 individuals. Among them, it has been reported that 241 individuals with HA had FVIII inhibitors (15.12%). Furthermore, among 241 individuals with HA and factor VIII inhibitor, 162 individuals had low titer of inhibitor while 51 cases had high titer of inhibitor.

Figure 1: The geographical distributions of surveys have been carried out on factor VIII inhibitor in various provinces in Iran.

Discussion

The World Federation of Hemophilia (WFH) recommends to screening of FVIII inhibitor every 3 months [13]. This shows the importance of early detection of FVIII for better managing and monitoring FVIII inhibitors in individuals with HA. The current review showed that FVIII inhibitors have not paid attention completely in Iran, or at least the results of surveys have not been published in international or regional journals.

In addition the results of published contributions showed that inhibitors developed in various frequencies in any part of the country, and each province would have a look and a survey on its status. The results of surveys in any part cannot be extended to other regions. This may be due to multi-factorial entity of inhibitor development [11].

It has been demonstrated that FVIII inhibitors don't increase frequency of bleeding episodes, but the control of hemorrhagic conditions in HA with inhibitors are more challenging. The amount of coagulation FVIII concentrates needs for managing bleeding in HA with inhibitor may be higher compared to control of bleeding with the same degree in HA without inhibitor. This means further financial burden for heath system.

The recommended methods for detection of FVIII inhibitors by International Society of Thrombosis and Hemostasis (ISTH) in Nijmegen assay due to better detection of low titer inhibitor comprised to Bethesda assay [19]. The findings showed that hemostasis laboratories have not shift from Bethesda assay to Nijmegen assay (Table 1) and this demonstrate necessity of an educational program for establishing better assay.

Conclusion

As a result of importance of FVIII inhibitor and in the other hand, existing gap on frequency of FVIII inhibitor in various part of Iran, it was tried to cover current gap. Such these data are useful for health providers and policy making decision managers to better forecasting future need of coagulation products not to encounter unexpected situations in treatment of individuals with HA.

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