Short Communication

Evaluation of inhibitor antibody in hemophilia A population

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Received: 31 Dec 2012
Revised: 13 Feb 2013
Accepted: 25 Feb 2013

Abstract

Background: Inhibitor antibody to exogenous Factor VIII (FVIII) is a major complication of hemophilia treatment. This study was conducted to determine the prevalence of inhibitor antibody directed against FVIII.

Methods: From May 2010 to May 2011, 52 patients with severe hemophilia A admitted in Amirkola Children's Hospital were evaluated. Those who had abnormal mixing study, antibody against FVIII were measured. Data were collected and analyzed.

Results: The age range of the patients was 4-60 years. The inhibitor antibody was seen in 9 (17.3%) patients. The mean age of patients with inhibitor at the time of diagnosis was 10.22 years (ranged 4-31 years). Old patients had more hemarthrosis than young patients. The mean level of inhibitor antibody was 8.47 Bethesda unit (ranged 2.3-29). Six patients had inhibitor antibody level ≥5 Bethesda unit and three patients had inhibitor antibody level <5 Bethesda unit.

Conclusion: This study showed that the prevalence of inhibitor antibodies in young patients is more than the old patients.

Keywords: Inhibitory antibody, concentrated FVIII, hemophilia A, Hemarthrosis

Caspian J Intern Med 2013; 4(3): 727-730

A hereditary bleeding disorder is caused by deficiency of a coagulation factor. Lack of factor VIII causes classic hemophilia (hemophilia A). The other types of hemophilia are caused by deficiency of factor IX (hemophilia B) or XI (hemophilia C) (1). Factor assays can be performed by the laboratory to determine the percentage of factors VIII, IX and XI compared to normal percentages (2-3). Hemophilia A is the most common type of hemophilia (4). Hemophilia A was classified based on serum level of factor VIII: less than 1 percent of normal (severe), 1–5 percent of normal (moderate), and more than 5 percent of normal (mild) (1). The hallmark of severe hemophilia is recurrent bleeding into joints and soft tissues with progressive joint damage. Prophylaxis has long been used in the United States but not universally adopted, because of medical, psychosocial, and cost controversies. Inhibitor antibody to exogenous FVIII is a major complication of haemophilia treatment (5). Clinical hallmark of inhibitor development is failure to respond to routine replacement therapy (6-7).

Some studies showed that the risk of inhibitor development is higher in patients treated with recombinant FVIII (rFVIII) than in patients treated with plasma derived FVIII (pFVIII) (8). Several data suggest that prophylaxis initiated at the early age might increase the risk of inhibitor formation (9). However, some studies showed that early exposure to factor VIII was not directly associated with higher incidence of inhibitor (10).The titer of antibody may be less than 5 Bethesda units (low responders) or excess of 5 Bethesda units (high responders).The clinical approach is different for these two groups (11-12). So, this study was conducted to determine the prevalence of inhibitor antibody directed against FVIII.

Methods

This descriptive and analytic study was done in Amirkola Children's Hospital from May 2010 to May 2011. Fifty two patients with severe hemophilia A admitted in Amirkola Children Hospital were evaluated. Other types of bleeding disorders such as hemophilia B, hemophilia C, von Willberand disease (vWD) type 3 and rare bleeding disorders were excluded. Consecutive patients with severe hemophilia A (FVIII ≤1 IU/ mL) were included. First monitoring for inhibitory antibody was performed with a mixing study at the time of study. In patients who had abnormal mixing study, antibody against FVIII was measured. Our laboratory used the Bethesda assay and a significant inhibitor titer was defined as being ≥1.0 Bethesda Unit (BU)/ mL on at least two consecutive measurements. High titer inhibitor was defined as having a titer of >5 BU/ mL at any time. The data were collected for each patient. The date of the first exposure to FVIII, the age of the child at the time of inhibitor development and the number of joint involvement were recorded. The data were collected and analyzed. The analysis of the parameters was performed using SPSS Version 18 with using chi-square test. All analyses were performed using a significance level of 5%.

Results

Fifty two severe hemophilia A patients were studied. The mean age of the patients was 22.33±1.99 years (ranged 4-60 years). FVIII level in all hemophilia A was ≤1 IU/ mL. The overall prevalence of inhibitor development (≥1.0 BU/ mL) was 9 of 52 (17.3%). In 6 patients (11.5%) the inhibitor level was 5 or more than 5 Bethesda units. The minimum level of inhibitors was 2.3 Bethesda units and maximum level was 29 Bethesda units (table 1).

Table1. Age of the patients and Level of Inhibitor antibodies

Age	Level of Inhibitor (Bethesda unit)
4	29
31	3
4	8
4	8
7	2.3
11	6
6	5
13	9
12	6

The mean age of patients with inhibitors was 10.22 years and the mean age of patients without inhibitors was 24.60 years (p=0.008).

Young patients started their first treatment with FVIII during the first month of life while the older patients had been treated with FVIII only at the time of bleeding. The older patients had irregular treatment. The patients without inhibitor suffered from at least one joint deformity more than the patients without inhibitor [3 of 9 (33%) versus 25 out of 43 (58%) respectively].

Discussion

Our study showed that the prevalence of inhibitor in hemophilia A (17.3%) is similar to the findings of other researchers (12-15). But it is more than that has been showed by Klukowska et al. (16). The product that was used in Klukowska et al.'s study was Octanate. Thus, we need to be more familiar with this product to use it. Our study showed that the production of inhibitor in young population was more than that in old patients. It may be due to the use of exogenous FVIII as prophylaxis in some young hemophilia A patients and the lack of use of any factor on demand in the older patients (17).

Conversely, Ociepa et al. showed that there are no differences in the development of inhibitor antibodies for those who received FVIII prophylaxis than those who did not (10). Mauser et al. believed that the risk for developing of inhibitor antibody in mild haemophilia A is increased with age (18). Other researchers also recommended that the major molecular defect of FVIII might be responsible of developing of inhibitor antibody (19-20). Initial treatment with recombinant FVIII and the presence of a major molecular defect was the most important variables affecting inhibitor development in some studies (21-22). We should revise the types of concentrated FVIII that were used in different periods in our center. Also, we should consider both inhibitor antibody formation and joint bleeding in hemophilia A to manage them. There is strong evidence in our study that prophylaxis preserves joint function in children with hemophilia A as compared to on-demand treatment (23).

In conclusion, our result showed that the prevalence of inhibitor antibody in young patients is relatively high like the report of other researchers. We believe further studies are needed to be done for the purification of F VIII product.

Acknowledgments

We are grateful to the hemophilia patients, the medical and nursing staff of the hemophilia center in Amirkola Children's Hospital for their cooperation, to Mrs Almasi, stuff of Non-Communicable Pediatric Diseases Research Center for typing the manuscript

Funding: This study was supported by the Vice-Chancellery of Babol University of Medical Sciences.

Conflict of interest: We have no conflict of interest to declare.

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