PREVALENCE OF INHIBITORS IN A POPULATION OF 1280 HEMOPHILIA A PATIENTS IN IRAN

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Abstacat- Development of inhibitor to factor VIII is the most serious complication of hemophilia therapy. To determine the prevalence of inhibitors in Iran hemophilia A patients exposed to blood products, 1280 hemophilia A patients (age range 9 months-84 years) were evaluated. All patients received several blood products such as fresh frozen plasma (FFP), cryoprecipitate, factor VIII. 635 of 1280 patients (49.6%), 277 patients (21.6%) and 368 patients(28.8%) had severe, moderate and mild disease, respectively. 184 of 1280 patients (14.4%) developed inhibitor. The prevalence of inhibitor for severe, moderate and mild in hemophilia A patients was 22.8%, 9.4%, 3.5% respectively. 41 patients (22.2%) and 143 patients (77.8%) were high responder and low responder respectively. Among 184 patients with inhibitor, 67 patients (36.4%) had blood group O and for B, A, AB blood groups, number of patients with inhibitor was 55 (29.9%), 50 (27.2%), 12 (6.5%) respectively and 153 patients (83.1%) had Rh blood group.

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INTRODUCTION

Factor VIII inhibitor development remains one of the most serious complications in the treatment of hemophilia A (1). There is an enormous difference in the incidince of inhibitor development in patients with different types of hemophilia (2-4). It is well known that patients with severe hemophilia A tend to develop inhibitors more than patients with mild or moderate hemophilia (5). Based on data reported worldwide, frequency of inhibitor in several retrospective studies is 5-10% (totally) and 10-15% in severe hemophilic patients (6). Some of these inhibitors were transient and low risk. Regular screening for such inhibitors and use of a more sensitive modification of the inhibitor assay contributed to the detection of a higher percentage of patients with inhibitors (7). In Iran, the majority of patients with hemophilia A have received several replacement therapies such as cryoprecipitates, fresh frozen plasma (FFP) and factor VIII. In Iran, there has been no study on the prevalance or incidence of inhibitor development in patients with hemophilia A. The primary aim of this study was to determine the prevalance of inhibitor formation in 1280 hemophilia A patients in Iran hemophilic center.

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MATERIALS AND METHODS

Patients: One thousand, two hundred and eighty patients (1280) with hemophilia A from 2950 patients in Iran attended our institute for investigations from 2000, 2001. These patients aged between 9 months and 84 years. They came from all states of Iran. Screening and assay of inhibitors in these patients were carried out in all patients once at the time of presentation to our center.

Methods: Screening of inhibitors was done by immediate correction of prolonged aPTT of the patient by a 1:1 mix of patient and normal pooled plasma (NPP), which was incubated for 2h and 4h along with simultaneous incubation of patient's plasma and NPP separately for the same length of time at 37°C. aPTT was then performed on the mix and on the separate patient's plasma and NPR any of the mix samples showing more than 10 prolongation of aPTT compared to the corresponding NPP were evaluated by inhibitor assay. The inhibitor assay used was the Nijmegen modification of the Bethesda assay in duplicate and the results were exposed as bethesda units (Bu) ml-1 (8).

RESULTS

From 1280 patients in our study, 635 patients (49.6%), 277 patients (21.6%) and 368 patients (28.8%) had severe, moderate and mild hemophilia A, resectively. 184 patients (14.4%) developed inhibitor.

145 patients of 635 with severe hemophilia A (22.8%), 26 patients of 277 with moderate hemophilia A (9.4%) and 13 patients of 368 with mild hemophilia A (3.5%) developed inhibitor (Table 1). From 184 patients with inhibitor, 41 patients (22.2%) and 143 patients (77.8%) were high responders and low responders, respectively. In 145 severe hemophilia A patients with inhibitor, 37 patients (25.5%) were high responders but in 26 and 13 moderate, mild hemophilia A patients with inhibitor, only 2 patients (7.69%) and 2 patients (15.3%) were high responder. In nine families, more than one member developed inhibitors. All members of these families had severe hemophilia A and in two families titer of inhibitor was high. Overally the level of inhibitor in patients varied from 0.4-113 Bu ml-l and in each group of hemophilia A patients were as follows: severe (0.4-113 Bu ml-l) Moderate (05-30 Bu ml-1), mild (05-15 Bu ml-l). Among 1280 patients, 724 patients (57.9%) were evaluated for development of inhibitor along 10 past years for several times.

613 patients from 724 (82.7%) had not devoloped inhibitor, in past, and in this study, inhibitor in these patients was negative also. Fifty seven patients (7.7%) from 724 had not developed inhibitor in past but in our study, were low responders. Fourteen patients (1.9%) from 724 had not developed inhibitor in past but in our study, were high responders. Forty one patients (5.5%) from 742 were low responder in past, but in our study, in 18 patients (2.4%), inhibitor disappeared, in 19 patients (2.5%) remaining low responders and in four patients (0.5%) level of inhibitor increased to high responder. 17 patients (2.2%) were high responder in past, but in our study, 10 patients(1.3%) remained high responders, in 6 patients (0.8%) level of inhibitor decreased to low responders and in one patient (0.11%), inhibitor disappeared. Overally, in 19 patients from 724 patients' (2.5%), inhibitor was transient and in 39 patients (5.2%), inhibitor was persistent. Among 184 patients with inhibitor, 67 patients (36.4%) had O blood group and 55 (29.9%), 50 (27.2%) and 12 (6.5%) had B, A and AB blood groups, respectively. 153 patients (83.1%) had Rh blood group. All patients with development of inhibitor received different blood products for treatment such as cryopreciptate, fresh frozen plasma, whole blood and Factor VIII (highly or intermediate purified).

DISCUSSION

In this first report on inhibitor development in a large number of patients from Iran with hemophilia, several interesting observations could be made. This study showed that overall prevalance of inhibitor was 14.4%, and inhibitor prevalance in severe hemophia A patients was 22.8%, a figure close to those reported in the literature (1,3,9-11). Inhibitor ptevalance in moderate and mild hemophilia was 9.4%, 3.5% respectively, and overal, 93 percent of patients with inhibitor were severe and moderate hemophilia A patients, that was compatible with other studies (12).

This high percent of inhibitor in these two groups is explained by more exposure to different blood products.

One interesting observation was development of inhibitor in mild hemophilia A patients group (3.5%). This is a rare occurrence that in similar study inhibitor in mild hemophilia A has not been detected (13,14).

Among, our patients with inhibitor, 22.2% were high responders but in similar studies results have been higher (14-16).

The prevalance of high responders was highest in severe hemophilia A patients. There may be several reasons for the low prevalance of high responders in this study: our patients received fairly infrequent blood support and most of our patients received FFP, cryoprecipitate or whole blood, which have much less potential to induce factor VIII inhibitors than highly purified factor concentrates as shown by Yee Tt. study (l7). The most and least common blood groups in patients with inhibitor were O and AB blood groups, and 83.1% had Rh blood group, compatible with blood group frequency in general population (18). The comprasion between prevalence of inhibitor and blood group had not been done already.

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