
Acquired Hemophilia in Pediatric Population

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ABSTRACT

The development of acquired inhibitors against the factor VIII protein in childhood period, is a very rare disorder in nonhemophiliac persons but may be clinically important condition due to potential serious bleedings. We have investigated acquired hemophilia development frequency in children with potential high risk groups. Totally 483 nonhemophiliac children including healthy controls were enrolled the study. Age range was 2 to 20 years and mean age was 11 ± 5.4 years. Risk groups for acquired hemophilia were selected among sick children with transfusion dependent β -thalassemia major (n= 75), children with malignancy (n= 55), asthma bronchiale (n= 65), type I insulin dependent diabetes mellitus (n= 63), collagen tissue disorders (n= 35). Age-matched 190 healthy children were selected as for healthy control group. Inhibitor tests were performed by the method of Bethesda assay. We have found only two patients who had acquired factor VIII inhibitor among 483 children. These two patients were solid tumor (osteosarcoma) and type I insulin dependent diabetes mellitus. Other risk groups and healthy controls have not inhibitor positivity. As a conclusion, acquired inhibitors should be considered for the differential diagnosis of unusual bleeding episodes in patients who had risk factors of all age groups including childhood period.

Key Words: Inhibitor, Hemophilia, Acquired hemophilia, Antifactor VIII antibody.

Turk J Haematol 2002;19(2):199-202

INTRODUCTION

The development of factor VIII inhibitors remains the most serious, life-threatening and most expensive complication of factor VIII therapy. Developing an inhibitor is one of the worst things that can happen to a patient with hemophilia. These patients suffer more se-

rious bleeding complications and they have greater disability, and incredible expenses^{1,2}.

However, development of acquired inhibitors against the factor VIII protein in childhood period, is a very rare disorder in nonhemophiliac persons but may be clinically important condition with a high mortality rate

due to potential life-threatening bleedings^[3-8]. Acquired inhibitors, called “acquired hemophilia”, have a very low incidence like as one per million population annually. Most of the patients occur in adults and are associated with autoimmune disorders, postpartum period, malignancy and after drug use^[4-6]. In this present study, we have investigated acquired hemophilia development frequency in children among potential high risk groups.

MATERIALS and METHODS

Totally 483 nonhemophiliac children including healthy controls were enrolled the study. Age range was 2 to 20 years and mean age was 11 ± 5.4 years and 256 patients were male (Table 1).

Risk groups for acquired hemophilia were selected among sick children with transfusion dependent β -thalassemia major (n= 75), children with malignancy (n= 55) (leukemia= 20, solid tumors= 35), asthma bronchiale (n= 65), type I insulin dependent diabetes mellitus (n= 63), collagen tissue disorders (n= 35) (juvenile rheumatoid arthritis, lupus erythematosis, dermatomyositis).

Age-matched 190 healthy children were selected as for healthy control group. Their age range was 2-15 and mean age was 10 ± 4.5 . Half of them was male (Table 1).

Citrated plasma samples were taken and stored in -80 degrees until testing. All samples were thawed and assayed in one day. Inhibitor test was performed by the method of Bethesda assay^[9].

RESULTS

We have found only two patients who had acquired factor VIII inhibitor among 483 children. The diagnosis of these two patients were solid tumor and type I insulin dependent diabetes mellitus. In healthy control group, no patient had acquired antifactor VIII antibody. In the patient groups with β -thalassemia major, asthma bronchiale and collagen tissue disorders, any patient was found inhibitor positivity.

Patients with acquired inhibitors: The first child with acquired inhibitor was a cancer patient with osteosarcoma. She was 14 year old girl. Before initiating the chemotherapy including high dose methotrexate and Adriablastin, she had 4 Bethesda units per mL titer of inhibitor. Her only clinical finding was ecchymosis in the skin. After chemotherapy courses, inhibitor was disappeared within four months. Monthly inhibitor titration was done and results were as follows: 4 BU/mL, 2 BU/mL, 1 BU/mL and 0 BU/mL, respectively. The second child with inhibitor was 16 year old girl and followed up the diagnosis with insulin dependent type I diabetes mellitus since 5 years. Her first inhibitor titer was 8 BU/mL. After one year inhibitor was disappeared without special treatment. She had never bleeding symptoms in their last 3 years of follow up.

DISCUSSION

Although acquired hemophilia A is a rare condition, associated bleeding episodes are often severe and carry a high risk of mortality^[3-5]. In contrast to the “well-known” inhibitors of hemophilia, inhibitors found in non-hemophiliacs occur predominantly in adults, usually over age 50^[1-3]. Acquired inhibitors generally do not appear to be related to previous exposu-

Table 1. Acquired hemophilia development in pediatric risk groups

Risk groups	n	Inhibitor frequency (%)
Transfusion dependent β -thalassemia	0/75	0
Asthma bronchiale	0/65	0
Collagen tissue disorders	0/35	0
Diabetes mellitus (type I)	1/63	1.5
Children with cancer	1/55	1.8
Healthy children	0/190	0
Total	2/483	

re to blood or blood products and in 50% of cases the associated disorder is rheumatic disease^[4]. We, as pediatric hematologists, suggested that the incidence of acquired inhibitors should also be investigated in the pediatric age group. Of course, only high risk groups should have selected since the condition is otherwise very rare in the pediatric age groups^[4-5].

Sometimes clinicians have unsolved bleeding problems in the clinical setting. Moreover, pediatric hematologists have similar kinds of associated disorders in pediatric practice as adult hematologists. Collagen tissue disorders is very common in pediatric practice such as rheumatic arthritis, lupus and rheumatic fever. In bleeding problems for these group acquired inhibitor development may occur and should be screened if necessary. However in present study there was no inhibitor patient in our children with collagen tissue disorders. Solid tumors are the most risky groups for inhibitor development among cancer patients^[4]. We have also one inhibitor patient who diagnosed with osteosarcoma. Rhodes et al, reported in a patient with carcinoma of the pancreas that after initiating chemotherapy acquired antibody was disappeared just like as in our case^[10]. After high dose of methotrexate therapy, inhibitor of our patient has disappeared within 4 months without significant clinical bleedings.

Some patients with multi-transfused blood products like as transfusion dependent thalassemia should have carried inhibitor development risk. However, as far as we know no thalassemic case was reported for acquired hemophilia in the literature. We have also no inhibitor patient in our thalassemic group.

Some patients with acquired inhibitor are characterized by severe hemorrhages. Sohngen et al, reported ten nonhemophilic patients from Germany^[11]. In his most patients, a sudden bleeding tendency was observed shortly after an injury or surgery. Four out of the ten inhibitor patients had asthma bronchiale and two patients had lupus erythematosus. However no patient have acquired inhibitor in our 65 patients with asthma bronchiale.

It has been well known that insulin-dependent diabetes mellitus is one of the most important autoimmune disorders in the children. In also our patients group, we determined acquired F VIII antibody in one child with type I diabetes mellitus. However this case had no

significant bleeding diathesis and one year after inhibitor spontaneously disappeared.

Some medications such as penicillin and sulfonamids were reported for responsible inhibitor occurrence^[4].

On the contrary of hemophilic inhibitors, there is considerable anecdotal experience with the use of steroids, cyclophosphamide, azathioprin, and more recently, cyclosporin in the management of inhibitors^[12-15]. These drugs have been recommended singly and in combination in order to elimination antifactor VIII antibody^[12]. If these patients have serious bleeding episodes, recombinant factor VIIa (Novo-Seven), activated or nonactivated prothrombin concentrates (PCC or APCC) (Kaskadil or FEIBA) and porcine F VIII concentrate (Hyate-C) can be used for obtaining efficient hemostasis^[6,11].

As a conclusion, acquired inhibitors should be considered for the differential diagnosis of unusual bleeding episodes in patients who had risk factors of all age groups including childhood period. However since incidence is very rare in pediatric population that should be screened for the presence of inhibitors may restricted to those pediatric patients with autoimmune disease and/or malignancies, who suffer a severe bleeding diathesis.

ACKNOWLEDGEMENTS

We want to thank Drs. Mehmet Kantar, Savas Kansoy, Mahmut Coker, Sukran Darcan, Damla Goksen, Remziye Tanac, Esen Demir from Ege University Hospital and Murat Hizarcioglu, Ceyhan Dizdarer, Ferah Genel, Berhan Genc from Behcet Uz's Children Hospital for recruiting the samples among different groups. Without their efforts for obtaining blood samples this study would not be realized. We also appreciate for laboratory analysis for Bethesda Inhibitor tests to Laboratory technician Basri Bilenoglu for him kind and careful performance.

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