The Evaluation of the Joint Status of Hemophiliac Adults: Single Center Adult Hematology Clinic Experience

Hemofilic Erişkinlerde Eklem Durumunun Değerlendirilmesi: Tek Merkez Erişkin Hematoloji Kliniği Deneyimi

**ABSTRACT**

**Objective:** Hereditary hemophilia A is the result of genetic alterations that cause deficiencies in clotting factor VIII, obstructing the process of hemostasis and predisposing hemophiliacs to spontaneous or post-traumatic bleeding. The aim of this study was to identify the target joint conditions of adult hemophilia A patients followed in adult hematology outpatient clinic. **Material and Methods:** We analyzed the target joint of 33 patients followed as hemophilia A in adult hematology outpatient clinic between 2000 and 2018 years. **Results:** Knee joint was the predominant joint affected by hemarthrosis in 57.5% cases. Ankle joint was involved in 42.4% cases and elbow joint was involved in 27.2% cases. Hip joint and shoulder joint involvement was seen in 9% and 6% cases, respectively. 48.5% of hemophilia A patients had developed target joint. Knee joint was the predominant target joint in 56.2% cases and ankle joint was the target joint in 18.8% cases. In this study, a positive association was observed between inhibitor presence and target joint development. Inhibitor was detected in 5 of 6 patients who developed target joint. **Conclusion:** In conclusion, the most affected joints were knee, ankle and elbow joints. Prophylaxis in patients with severe hemophilia may be planned earlier because of the more frequent occurrence of target joint development.

**Keywords:** Hemophilia; hemophilic arthropathy; target joint

**ÖZET**

Kalıtsal hemofili A, pıhtılaşma faktörü VIII eksikliğine yol açan genetik değişikliklerin sonucudur, hemostaz sürecini engeller ve hastalarda spontan veya travma sonrası kanamaya sebep olur. Bu çalışmanın amacı, erişkin hematoloji polikliniğinde izlenen erişkin hemofili A hastalarının hedef eklem durumlarını değerlendirmektir. **Gereç ve Yöntemler:** Çalışmada, 2000-2018 yılları arasında Hacettepe Üniversitesi Hastanesi’nde izlenen erişkin hematoloji polikliniğinde hemofili A ile takip edilen 33 hastanın hedef eklem durumları değerlendirildi. **Bulgular:** Diz eklemi, %57,5 olguna hemartrozdan en sık erkenen eklemdi. Ayak bileği eklemi %42,4 olguna, dirsek eklemi %27,2 olguna etkilenmişti. Kalça eklemi ve omuz eklemi tutulumu sırasıyla %9 ve %6 olguna sıralandı. Hemofili A hastalarının %48,5 inde hedef eklem gelişti. Diz eklemi %56,2 olguna en sık izlenen hedef eklemdi ve %18,8 olguna ise ayak bileği eklemi hedef eklemdi. Bu çalışmada, inhibitör varlığı ve hedef eklem gelişimi arasında pozitif bir ilişki olduğu gözlandi. Hedef eklem gelişen 6 hastanın 5’inde inhibitör saptandi. **Sonuç:** Sonuç olarak en fazla etkilenen eklemler diz, ayak bileği ve dirsek eklemleri idi. Ağır hemofil hastalarda profilaksi, hedef eklem gelişiminin daha sık görülmesi nedeniyle daha erken planlanabilir.

**Anahtar Kelimeler:** Hemofili; hemofilik artropati; hedef eklem

Hereditary hemophilia A is the result of genetic alterations that cause deficiencies in clotting factor VIII, obstructing the process of hemostasis and predisposing hemophiliacs to spontaneous or post-traumatic bleeding. The major clinical manifestation is intra-articular bleeding (hemarthrosis), which begins even in infancy. Hemophilic arthropathy is
caused by recurrent hemorrhage into joints and results in an arthritis. Hemophilic arthropathy is characterized by soft tissue changes due to proliferation and osteochondral changes due to subchondral erosions, cartilage loss, and cyst formation. Synovial inflammation contributes to recurrent joint hemorrhage in an affected joint, generally called a target joint, which accelerates the destructive process. Finally, bones and joints affected by hemophilic arthropathy develop osteoporosis, osteophytic growths, and fibrous contractures, severely limiting and disrupting mobility. In the past hemophilic arthropathy has affected 90% of adults with severe hemophilia and involved 1 to 6 joints. Hemophilic arthropathy causes chronic pain and functional limitation often necessitating chronic opioid dependence and multiple orthopedic procedures, including joint replacements and fusions. In addition to the great cost of replacement factor concentrate, hospitalizations, and joint replacements, the human cost of hemophilic arthropathy is loss of employment opportunities, less favorable insurance access, decreased social participation, and a high prevalence of depression. The aim of this study was to identify the target joint conditions of adult hemophilia A patients followed in adult hematology outpatient clinic. Additionally to evaluate the relationship between the presence of an inhibitor and the target joint development.

MATERIAL AND METHODS

STUDY DESIGN AND DATA COLLECTION

This study has been performed in a retrospective manner. All patients gave written informed consent for the procedure. We analyzed the target joint of 33 patients followed as Hemophilia A in adult hematology outpatient clinic between 2000 and 2018 years. All of the patients were >18 years. Demographic data of the patients, treatment data, average number of joint bleeding episodes in last 1 year, most affected joints in decreasing order of frequency and target joints (if developed), factor VIII level and inhibitor level were obtained from hospital database and from the patients. Target joint bleeding was defined as 4 bleeds/6 months.

STATISTICAL ANALYSES

Statistical analyses were performed using the SPSS software version 25. The variables were investigated using visual (histograms, probability plots) and analytical methods. Descriptive statistics were presented as mean±standard deviation for continuous variables, and categorical variables as number of patients and percent (%). The data used to support the findings of this study are available from the corresponding author upon request.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS

A total of 33 diagnosed cases of hemophilia A aged more than 18 years attending the adult hematology clinic were enrolled in the present study. All patients had hereditary hemophilia A. Median age of the patients was 45 (range, 21-72). Patients are classified as having severe (FVIII <1 IU/dL), moderate (FVIII 1-5 IU/dL), and mild hemophilia (FVIII >5 IU/dL). Fifteen patients (45.4%) had severe hemophilia, 11 patients (33.4%) had moderate hemophilia, 7 patients (21.2%) had mild hemophilia as shown in Figure 1. Inhibitor detected in 6 (18.1%) patients on heat inactivated plasma utilizing the Nijmegen modification of the Bethesda assay.

FIGURE 1: Distribution of severity in hemophilia A patients.
CLINICAL CHARACTERISTICS OF JOINT STATUS

Knee joint was the predominant joint affected by hemarthrosis in 57.5% cases. Ankle joint was involved in 42.4% cases and elbow joint was involved in 27.2% cases. Hip joint and shoulder joint involvement was seen in 9% and 6% cases, respectively. 48.5% patients of hemophilia had developed target joint. Knee joint was the predominant target joint in 56.2% cases and ankle joint was the target joint in 18.8% cases. Elbow and hip joint was target joint in 2 (12.5%) and 2 (12.5%) patients, respectively (Table 1). In this study, a positive association was observed between inhibitor presence and target joint development (Table 2). Inhibitor was detected in 5 of 6 patients who developed target joint (p<0.001). There was a positive correlation between the presence of frequent bleeding and the presence of inhibitor. Inhibitor positivity was detected in 5 patients with frequent bleeding and only one patient with no complaints of bleeding (p<0.001). The most common complaint of patients was pain of the joints and hemarthrosis (17 patients 51.5%). The most common complaint after pain of the joints and hemarthrosis was hematuria (3 patients 9%). Only one patient (3%) complained of anal bleeding. Twenty one patients (63.6%) were under prophylaxis. Twelve patients (36.4%) received on demand treatment. In our follow-up, all patients with hemophilia A were still alive. There was an association between hemophilia severity and target joint development (p=0.05) as shown in Figure 2. While 8 of the severe hemophilia patients developed the target joint, only 1 of the mild hemophilia patient developed the target joint. Radioactive synovectomy was performed in patients who developed a target joint.

**DISCUSSION**

In this study, 48.5% of hemophilia A patients developed target joints. Knee joint was the most common target joint in hemophilia A patients (56.2%). Then, it was observed that the target joint developed in the ankle (18.8%), elbow (12.5%) and hip.
(12.5%) joint respectively. Ankle joint was involved in 42.4% cases and elbow joint was involved in 27.2% cases. Hip joint and shoulder joint involvement was seen in 9% and 6% cases, respectively. This study showed an association between the presence of inhibitor and target joint development. Inhibitor was detected in 5 of 6 patients who developed target joint. There was an association between hemophilia severity and target joint development. While 8 of the severe hemophilia patients developed the target joint, only 1 of the mild hemophilia patient developed the target joint.

Joint disease remains the hallmark of hemophilia patients. Aledort et al. defined a 90% joint disease prevalence in severe hemophilia.\textsuperscript{4} One study demonstrated that patients with severe hemophilia experienced a mean of 15 bleeds/year and this arthropathy caused limitation of activity in at least 50% of affected patients.\textsuperscript{6} Severe hemophilia patients (<1% FVIII) are the most likely to manifest joint disease. It seemed that raising factor levels above this threshold by the use of regular or prophylactic infusions of factor concentrate might limit joint disease. Hirschman et al. demonstrated that maintaining FVIII levels of 2% was associated with reduced bleeding.\textsuperscript{7} A study in adults and adolescents showed a decrease in hemarthros is, and recommended structural joint protection with secondary and tertiary prophylaxis versus on demand, although the benefits were greatest when prophylaxis had been initiated early in childhood.\textsuperscript{8} Also, two studies showed that prophylaxis was effective in reducing joint bleeding and limiting joint damage. Patients continued to have bleeding during prophylaxis while also demonstrating radiographic progression.\textsuperscript{9,10} In one study, 68% cases of hemophilia patients had knee joint swelling followed by ankle joint (22%), elbow joint (14%), shoulder joint (8%), and hip joint involvement (6%).\textsuperscript{11} Similar results were observed in this study. In another study on hemophilia B patients, most commonly involved joint was found to be knee in 33.3%, followed by elbow in 17.7%, ankle in 13.3%, and hip joint in 4.5%.\textsuperscript{12}

The most important therapy related complication in hemophilia A replacement therapy with coagulation factor VIII products is the formation of neutralizing antibodies, termed inhibitors, affecting around 30% of severe hemophilia A patients.\textsuperscript{13} The presence of inhibitors causes replacement therapy to be ineffective, make bleeds difficult to prevent or treat and finally results in increased morbidity.\textsuperscript{14} The causes of inhibitor development are still not fully understood. The reason is multifactorial with both genetic and therapy-related risk factors.\textsuperscript{15,16} In this study, it was observed that the morbidity in-
creased with the development of inhibitors.

Our study had some limitations. First, this study was retrospective. Second the number of patients with hemophilia A included in this study was low. Third, only hereditary hemophilia A patients were included in the study. In conclusion, the most affected joints were knee, ankle and elbow joints. In the present setting 48.5% patients developed target joint. Knee joint was the predominant target joint followed by ankle joint. In the presence of inhibitor, target joint development is more common. Therefore, patients should be monitored for the development of inhibitors. Prophylaxis in patients with severe hemophilia may be planned earlier because of the more frequent occurrence of target joint development in patients with severe hemophilia.

**Conflicts of Interests**

The authors of this paper have no conflict of interests, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included. The data [SPSS and patients’ information] used to support the findings of this study are available from the corresponding author upon request.

**Role of the funding source**

None.

**Ethical approval**

All of the ethical considerations had been strictly followed in accordance with the 1964 Helsinki declaration. As a standard care/action of the our hospitals of the Medical School, it has been recognized from the patient records that all of the studied patients had given informed consents at the time of hospitalization and before the administration of treatment and other relevant diagnostic/therapeutic standard of care.

**REFERENCES**