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Original Article

Diagnostic evaluation of our patients with hemophilia A: 17-year experience

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Abstract

Aim: Hemophilia A is a rare inherited bleeding disorder resulting from factor VIII deficiency and is a group of diseases characterized by intra-articular and intramuscular bleeding. In this study, we aimed to retrospectively evaluate the treatment outcomes, demographic and clinical characteristics of our patients who were treated and followed up for last 17 years in our pediatric hematology unit with a diagnosis of Hemophilia A.

Material and Methods: The medical records of 83 patients who were diagnosed with Hemophilia A and followed up between 1997 and 2014 in our hospital's pediatric hematology clinic were reviewed retrospectively. The demographic data, prophylaxis state, development of inhibitors and clinical characteristics of the patients were evaluated.

Results: When the complaints at presentation were examined, it was found that 27 (32%) patients had hemarthrosis, 24 (29%) patients had ecchymosis and hematoma, 13 (16%) patients had prolonged bleeding after trauma or cut, 10 (12%) patients had gingival, mouth or nose bleeding, 4 (5%) patients had prolonged bleeding after circumcision, 4 (5%) patients had gastrointestinal bleeding, 1 (1%) patient had hematuria. Fifty (60%) patients were considered severe hemophilia A, 20 (24%) patients were considered moderate hemophilia A and 13 (16%) patients were considered mild hemophilia A according to factor activity. Among severe hemophilia A patients, primary prophylaxis was being administered in 2 (2%) patients and secondary prophylaxis was being administered in 40 (48%) patients. Inhibitor positivity was found in 8 (10%) of these patients. It is found that hemophilic artropathy developed in 17 patients and 8 of these 17 patients had undergone radioisotope synovectomy.

Conclusions: Treatment of severe bleeding in hemophilia A patients should be performed in hospital and the presence of inhibitor must be investigated in cases of uncontrolled bleeding where adequate doses of factor concentrates have been administered for treatment. In order to decrease the development of inhibitor, prophlaxis should be suggested to patients rather than repetetive treatment when bleeding occurs. The radioactive synovectomy should not be overlooked in countries like ours in which factors can not be used adequately. (Turk Pediatri Ars 2015; 50: 96-101)

Keywords: Bleeding, hemophilia, inhibitor

Introduction

Hemophilia A is a congenital X-linked recessive bleeding disorder. The factor VIII gene (FVIII) is localized on the long arm of the Xth cheomosome (Xq27). Hemophilia A is observed in approximately one in 5000 male births (1). Hemophilia A constitutes 80-85% of all hemophilia cases (2). Use of recombinant factors or plasma-derived factors instead of the deficient factor is an important treatment method for hemophilia patients (3, 4). Currently, the most common and serious complication in hemophilia treatment is production of allo-antibody (inhibitor) against the factor protein administered (5). The musculoskeletal system complications which are observed frequently in hemophilia include acute intraarticular bleeding, intramuscular bleeding, chronic intraarticular bleeding, chronic synovitis, chronic hemophilic arthropathy and fracture (6).

In this study, we aimed to retrospectively evaluate the demographic and clinical properties and treatment results of the patients with hemophilia A followed up in our pediatric hematology unit for 17 years.

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Material and Methods

The patients with a diagnosis of hemophilia A who were followed up and treated in Yüzüncü Yıl University, Medical Faculty, Pediatric Hematology Unit between 1997 and 2014 were included in the study. The files of 90 hemophilia A patients included in the study were examined retrospectively. A total of seven patients three of whom were diagnosed in our unit and followed up in another center and four with a lack of necessary information in the files were excluded from the study. The patients were divided into three groups according to factor activity. A factor acitivity of <1% was defined " severe hemophilia", a factor activity of 1-5% was defined as "moderate hemophilia" and a factor activity of >5% was defined as "mild hemophilia". Continuous treatment initiated before the second articular bleeding and before the age of two years in the absence of clinical and radiological joint damage was defined as primary prophylaxis. Prophylaxis initiated after two or more articular bleedings before joint damage develops was defined as secondary prophylaxis (7). Inhibitor screening was performed with Bethesda method. The threshold value was considered to be 0,6 BU/mL. The values above this threshold were considered positive and the values below this threshold were considered negative. An inhibitor titer of >5 BU/mL was considered high titer and an inhibitor titer of <5 BU/mL was considered low titer (2). Inhibitor is measured regularly every 6 months in hemophilia A patients followed up in our pediatric hematology unit. In addition, inhibitor is measured in cases of bleeding where intensive factor use is required or before any operation. In our center, patients who have at least 2-3 bleeding attacks monthly despite medical treatment in the absence of radiological findings of irreversible joint damage are considered ideal candidates for radioactive synovectomy (RAS). Radioactive synovectomy was performed in our patients using Y-90 (Yitrium-90) as the radioisotope substance in İstanbul University Cerrahpaşa Medical Faculty, Ege University Medical Faculty and Çukurova University Medical Faculty and intraarticular steroid injection was not performed after the procedure. The patients were divided into three groups by age groups as 1-3 years, 4-10 years and 11-18 years. Approval was obtained from the ethics committee of Yüzüncü Yıl University Medical Faculty on 01.22.2014 with number 01.

Statistical analysis

Descriptive statistics were expressed as figures and percentages. In cases where the distribution range was too wide, the median value was given as a measure of central tendency.

Results

The median age of presentation of 83 patients who were followed up with a diagnosis of hemophilia A was 61 months (4-180 months). All patients were male. When classified by age range, 11 patients (13.3%) were in the 1-3 year age group, 35 patients (42.1%) were in the 4-10 year age group and 37 patients (44.6%) were in the 11-18 year age group. When the presentation complaints of our patients were evaluated, 27 patients (32%) had intraarticular bleeding, 24 patients (29%) had ecchymosis and hematoma, 13 patients (16%) had uncontrolled bleeding following trauma and cut, 10 patients (12%) had gingival bleeding, oral bleeding and epistaxis, four patients (5%) had gastrointestinal bleeding and 1 patient (1%) had hematuria. The presentation complaints by age groups are shown in Table 1. At first presentation, local hemostatic agents were used especially in patients with active mucosal bleeding or active bleeding following trauma and cut. Afterwards, fresh frozen plasma was given to the ones whose bleeding could not be stopped. At the first presentation, familial history was not found in 36 (43%) patients. According to factor activities, 50 (60%) patients were consideed to have severe hemophilia, 20 (24%) patients were considered to have moderate hemophilia and 13 (16%) patients were considered to have mild hemophilia. Primary prophylaxis was initiated in two (2%) patients and secondary prophylaxis was initiated in 40 (48%) patients. Six patients (7%) who received secondary prophylaxis did not regularly attend outpatient follow-up visits and secondary prophylaxis was proposed to one patient, but the family refused. The group who received treatment when bleeding occured included 41 patients (49%); prophylaxis could not be given because of treatment non-compliance. None of the patients had cen-

Table 1. Complaints at presentation by age groups in our patients

Complaint	1-3 years n (%)	4-10 years n (%)	11-18 years n (%)
Hemarthrosis	8 (9.6)	9 (10.8)	10 (12)
Ecchymosis and hematoma	10 (12)	8 (9.6)	6 (7.2)
Unstoppable bleeding following trauma	3 (3.6)	6 (7.2)	4 (4.8)
Oral mucosal bleeding	5 (15.6)	2 (%2.4)	3 (3.6)
Unstoppable bleeding following circumcision	4 (4.8)	-	-
Gastrointestinal bleeding	1 (1.2)	1 (1.2)	2 (2.4)
Hematuria	-	-	1 (1.2)

Table 2. The properties of the patients with high titer inhibitor

	Patient number					
	1	2	3	4	5	6
Age at the time of diagnosis	14 months	4 years	1.5 years	2 years	7 years	7 months
FVIII level (%)	<1%	<1%	<1%	<1%	<1%	<1%
Inhibitor level (BU)	15	16	6	14	12	11
Factor which was used before inhibitor	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
Day of usage of factor before inhibitor	30	26	21	24	23	20
Area of severe bleeding	None	None	None	Iliopsoas	None	GIS
Prophylaxis status	aPCC	aPCC	aPCC	aPCC	rFVIIa	aPCC

aPCC: active prothombin complex concentrate; BU: bethesta unit; GIS: gastrointestinal system; rFVIIa: activated recombinant FVII

tral venous catheter or port. Bleeding and injury constituted the most common complaints at presentation to the emergency outpatient clinic with a rate of 69%.

The rate of inhibitor positivity was found to be 9.6% in our patients. The inhibitor levels in 8 patients with inhibitor positivity were as follows: 2 BU, 4 BU, 6 BU, 8 BU, 11 BU, 12 BU, 15 BU and 16 BU. All our patients who developed inhibitor had severe hemophilia and were treated with antihemophilic factor previously. All our patients who developed inhibitor were in the group who did not receive prophylaxis before and who received treatment whenever bleeding occured. In these patients, inhibitor development was found to range between 20 and 30 factor usage days. Two (25%) of our inhibitor positive patients were treated with recombinant FVIII preparation and 6 (75%) were treated with plasma-derived factor VIII preparations. During the follow-up period, the inhibitor titer did not exceed 5 BU/mL in two of our patients and this was evaluated to be "low titer inhibitor". In the follow-up of these patients with low titer inhibitor whose therapies were continued with plasma-derived FVIII preparations, the inhibitors disappeared spontenously. Activated recombinant FVIII (rFVIIa) was given to one patient with high titer inhibitor at a dose of 90 mcg/kg two days a week for secondary prophylaxis and activated prothrombin complex concentrate (aPCC) was given to 5 patients at a dose of 50 U/kg three days a week. In all these patients, target joint was present and hemophilic artropathy was developed. The patients who were found to have high titer inhibitor are shown in Table 2. Gastrointestinal bleeding had occured before inhibitor was found in one of these patients and iliopsoas bleeding had occured in the other one and Intensive factor treatment had been given to both. In the other four patients, intensive factor treatment was not administered before inhibitor development. Radioactive synovectomy was applied in the right knee and left knee joints without complications in a patient who developed chronic synovitis and who had positive inhibitor. It was notice that RAS was applied for the second time in the right knee joint in the same patient one year later. Hemophilic artropathy was found in 6 patients who had high titer inhibitor and in 11 patients who received secondary prophylaxis. Radioactive synovectomy was applied in 8 of these patients. The severe bleeding attacks which were found in the follow-up of our patients included iliopsoas bleeding in four patients, hematuria in three patients, intracranial bleeding in one patient, pretracheal bleeding in one patient, gastrointestinal bleeding in four patients and compartment syndrome in one patient (Table 3). Intracranial bleeding occured following trauma at the age of 20 years and fresh frozen plasma was used in treatment in the years when factor products were not available in our country.

Table 3. Severe bleedings which were observed in the follow-up

Bleeding region	n (%)
Hemophilic artropathy	17 (20)
Right knee	9 (52)
Left knee	8 (48)
Iliopsoas bleeding	4 (4.8)
Hematuria	3 (3.6)
Intracranial bleeding	1 (1.2)
Pretracheal bleeding	1 (1.2)
Gastrointestinal bleeding	4 (4.8)
Compartment syndrome	1 (1.2)

Discussion

Hemophilia is an inherited life-long chronic hematological disease. Although it is a rare disease, life-long bleeding disorder and being dependent on expensive

blood products provided from abroad in terms of treatment increase the importance of this disease. Hemophilia and especially joint problems affect the patient's life negatively in terms of physical, social and emotional aspects. The clinical findings of the disease emerge as the baby grows up and especially as he starts to crawl and walk. As the severity of the disease increases, the age of diagnosis is moved to an earlier time and the clinical findings are experienced with a higher degree of severity. Therefore, patients with mild hemophilia are usually diagnosed at more advanced ages, since bleedings occur as a result of more severe traumas or surgical interventions.

Inhibitor is found in 25-30% of severe hemophilia A patients and in approximately 5-15% of moderate hemophilia A patients (8). Kavaklı et al. (9) screened 1057 hemophilia A patients in a multi-center study conducted in the whole of Turkey and reported persistent inhibitor developed with a rate of 11.2% in the whole hemophilia A group and with a rate of 15.8% in the severe hemophilia A group after exclusion of the patients who were found to have transient inhibitor. It was observed that inhibitor developed in 8 patients with severe hemophilia A among 83 hemophilia A patients evaluated in our study and the frequency was found to be 9,6%. Since development of inhibitor is the most common and severe treatment complication at the present time, unnecessary FVIII treatment is avoided especially in the early infancy period in our clinic to prevent inhibitor development. If use of FVIII is required, "primary prophylaxis" program is initiated without waiting for development of joint bleeding or other severe bleedings.

Prophylaxis in severe hemophilia A patients aims to prevent joint disabilities, life-threatening bleedings and hospitalizations and to increase the quality of life of the patient and family (10). In the study of Ljung et al. (11), primary prophylaxis was given to 75 of 121 patients and it was reported that joint damage occured with a significantly lower rate in this group compared to the other groups. Gringeri et al. (12) compared prophylaxis in 21 patients aged between 1 and 7 years with severe hemophilia A without clinical and radiological finding of joint damage who had at least one joint bleeding in the last 6 months and treatment whenever bleeding occured in 19 patients. The frequency of bleeding was reported to be 0,2/month in the group who received prophylaxis and 0.52/month in the group who received treatment whenever bleeding occured. In the study of Lucia et al. (13), proven hemophilic artropathy in severe hemophilia A patients was found with a rate of 3.3% in the group who received primary prophylaxis and with a rate of 37.8% in the group who received secondary prophylaxis. The authors reported that joint damage could be prevented in the long-term with early initiation of prophylaxis in patients with severe hemophilia A. In our study, it was observed that two patients received primary prophylaxis and 40 patients received secondary prophylaxis. Clinical and radiological findings of joint damage were not found in our patients who received primary prophylaxis, whereas hemophilic artropathy was found in 17 (42.5%) patients who received secondary prophylaxis. Since the mean age at presentation was 67 months in our patients, the number of the patients who received secondary prophylaxis was significantly higher compared to the number of the patients who received primary prophylaxis. In the study of Santagostino et al. (14), it was reported that a 70% decrease occured in inhibitor development in the children in whom the mean age of initiation of prophylaxis was 35 months. Similar results were also demonstrated in a multi-national larger study. In this study, it was reported that regular prophylaxis inititated in the early period of life was associated with a 60% lower risk of development of inhibitors than whenever bleeding occured treatment (15). In our study, it was found that all our patients who developed inhibitor were in the group who were received treatment whenever bleeding occured and who did not receive prophylaxis.

RAS which is an easy, inexpensive, noninvasive interventions which requires only a short hospitalization time and which can be repeated when necessary is a valuable treatment method for developing countries in which factor can not be used sufficiently including our country in preventing joint diabilities. The basic rationale of the procedure is to create fibrosis in the fragile and hypertrophic synovial tissue which causes to frequent bleedings by giving "radioactive isotope" into the intraarticular synovial space. Various enzymes released from the synovial tissue and fluid lead to joint damage by causing to cartilage destruction. Creating fibrosis in the area in question is efficient in treatment (16). Zülfikar et al. (17) performed RAS in 60 joints (27 knees, 16 ankles, 15 elbows and two shoulders) of 39 patients 37 of whom had hemophilia A, one of whom had hemophilia B and one of whom had acquired hemophilia with a median age of 16 years and reported that they obtained successful results with a rate of 80%. Kavaklı et al. (16) performed RAS in a total of 190 joints in 107 patients with severe hemophilia A and 20 patients with severe hemophilia B within 6 years and found a decrease in the mumber of bleedings and in factor consumption in a three-year follow-up period after RAS. They reported that no bleeding attack was found in 50% of the patients

in the first year in the follow-up. RAS was performed in 10 joints in our 8 patients who diagnosed severe hemophilia A and they were followed up for a mean period of 9 months (4 months-2 years). No adverse condition was observed in our patients during the procedure and follow-up and the number of bleedings in the target joint decreased by 50% in all patients.

Approximately 1/3 of hemophilia patients do not have a familial history and they have spontaneous de novo mutations. Therefore, absence of a familial history does not exclude the possibility of hemophilia (18, 19). Kasper et al. (20) examined the family tree of 804 hemophilia patients and found that a positive familial history was present with a rate of 79% in the patients with mild and moderate hemophilia A and with a rate of 45 % in the patients with severe hemophilia A. In our study, a positive family history was not found in 36 (43%) patients and a positive familial history of hemophilia A was found in 47 (57%) patients.

Ciscumcision is applied almost by all of our population as a very important element of the sociocultural life. In a study conducted in our country, approximately 80% of the children with hemophilia and their families stated that not being circumcised was a disgraceful state in the community (21). In the study of Zülfikar et al. (22) conducted between 1996 and 2003, it was emphasized that the period between 6 months and 18 months when the body weight and the inhibitor risk are low should be preferred for circumcision of hemophilic children. In different studies, bleeding complication related with circumcision in healthy boys has been reported with a rate of 0.1-35% (23, 24). Severe bleeding has been reported only in 10% of the cases (25). Our four patients were diagnosed with hemophilia A because of prolonged bleeding following circumcision performed at the age of 1-3 years.

In hemophilia patients, the intracranial region is the most feared bleeding region and intracranial bleeding is the most important reason of morbidity and mortality. In cases of this type of bleedings, factor should be initiated urgently at appropriate doses for an appropriate period without waiting for clinical and radiological evaluation. All head traumas and severe headaches should be urgently treated as if intracranial bleeding is present. Factor VIII should be initiated immediately at a dose of 50 IU/kg (such that the factor level is 80-100%). Subsequent doses should be adjusted according to imaging results (computarized tomography/magnetic resonance). Patients with head trauma should be carefully followed up in terms of bleeding also in the late period. In presence of severe headache without trauma, intracranial bleeding should be absolutely considered. Intracranial bleeding may occur in patients with hemophilia without a history of trauma (26, 27). Intracranial bleeding is observed with a rate of 3-10% after the neonatal period (28). In the study of Özgenel et al. (29), it was reported that intracranial bleeding was observed only in 5 patients in a 5-year period. In our study, intracranial bleeding occured only in one patient following trauma. The patient who was given fresh frozen plasma for replacement was lost because of diffuse intraparenchymal brain hemorrhage.

In patients with hemophilia, iliopsoas bleeding may cause to shock by leading to excessive bleeding. If the diagnosis and treatment is delayed, the enlarged soft tissue mass compresses the adjacent nerve tissue and may lead to femoral nerve neuropathy (30). When thigh, hip and inguinal pain, flexion contracture in the hip, abdominal tenderness and limping occur in patients with hemophilia, iliopsoas bleeding should be considered. Prevention of complications is only possible with early diagnosis and treatment. In cases of bleeding into the iliopsoas muscle, the general treatment approach is replacement of the deficient factor and absolute bed rest until the bleeding stops. Replacement treatment should be continued until the bleeding is absorbed and an appropriate physical therapy program should be initiated (30, 31). Balkan et al. (32) found iliopsoas bleeding in 8 of 146 hemophilia patients whom they followed up for 7 years. Dauty et al. (33) found iliopsoas bleeding in 5 (0.29%) of 410 hemophilia patients whom they followed up for 5 years. Iliopsoas bleeding was found in four of our patients (4.8%).

Conclusively, follow-up and treatment of hemophilia A patients should be conducted in centers experienced in this area. All severe bleedings should be treated in the hospital and presence of inhibitor should be investigated in patients in whom bleeding can not be controlled despite use of appropriate dose of factor product and prophylaxis should be recommended to decrease inhibitor development instead of treatment whenever bleeding occurs. The option of synovectomy which is an easily applicable, inexpensive and noninvasive method and which can be repeated when necessary should not be ignored in countries where factor can not be used sufficiently including our country.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yüzüncü Yıl University Faculty of Medicine.

Informed Consent: Written informed consent was obtained due to retrospective nature of the study.

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