Comprehensive Assessment of Common Medical Problems in Adult Patients with Hemophilia A: A Single-Center Experience in Turkey

Erişkin Hemofili A Hastalarında Yaygın Tıbbi Problemlerin Kapsamlı Gözden Geçirilmesi: Türkiye'de Bir Tek Merkez Deneyimi

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ABSTRACT

Objective: Chronic age related medical problems and blood-borne viral infections may be overlooked by the clinicians in Hemophilia A, and likewise Hemophilia A patients may not be concerned sufficiently about their medical conditions other than hemophilia A. We aimed to investigate the comorbidities and the blood borne viral infections observed in the adult hemophilia A patients in our tertiary center.
Methods: Adult hemophilia A patients diagnosed between the years of 1961 and 2007 were reviewed retrospectively for analysis. Demographic data, comorbidities, body mass indexes and markers for viral infections were recorded.
Results: A total of 26 patients were in strict follow up in our Hemophilia A cohort. Hypertension (19%) and nephrolithiasis (19%) were the most common comorbidities. Being obese (Body Mass Index≥30 kg/m^2) was not found as a risk factor for diabetes (p=1.000), hypertension (p=0.280), and hepatosteatosis (p=0.546). Two cases had positive Hepatitis B virus and 2 had positive Hepatitis C virus load.
Conclusion: The results of our present study revealed that hypertension unawareness was high and incident diabetes is also a problem for Hemophilia A patients. Clinicians should be aware of blood-borne pathogens and other comorbidities; they should perform screening tests.

Keywords: Diabetes Mellitus, Hemophilia A, Hepatitis B virus, Hepatitis C virus, Hypertension, Obesity

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ÖZET

Amaç: Hemofili A hastalarında, kronik yaş ilişkili problemler ve kan yolu ile bulaşan viral enfeksiyonlar hekimlerin gözünden gözden kaçabildiği gibi, Hemofili A hastaları da hemofili dışındaki tıbbi durumları ile yeterince ilgili olmayabilirler. Bu çalışmada üçüncü basamak merkezimizdeki erişkin Hemofili A hastalarının yandaş hastalıklarını ve kan yolu ile bulaşan viral enfeksiyonlarını incelemeyi amaçladık.
Yöntem: 1961 ve 2007 yılları arasında tanı almış erişkin Hemofili A hastalarının verilerini retrospektif olarak inceledik. Demografik veriler, yandaş hastalıklar, vücut kitle indeksleri ve viral belirteçler gözden geçirildi.
Bulgular: Hemophilia A kohortumuzda toplam 26 hasta yakın izlemde idi. Hipertansiyon (%19) ve böbrek taşı (%19) en sık yandaş hastalıklardı. Obez olmak (Vücut Kitle İndeksi ≥30 kg/m^2); diyabet (p=1.000), hipertansiyon (p=0.280) ya da hepatosteatoz (p=0.546) için risk faktörü olarak bulunamadı. İki vaka pozitif Hepatit B virüsü ve 2 vaka da pozitif Hepatit C virüsü yüküne sahipti.
Sonuç: Çalışmamız hipertansiyonun farkında olmamanın yüksek olduğunu ve ayrıca yeni tanı diyabetin de Hemofili A hastalarında bir problem olduğunu göstermektedir. Hekimler kan yolu ile bulaşan virüslerin ve yandaş hastalıkların farkında olmalı; tarama testlerini yapmalıdırlar.

Anahtar Sözcükler: Diyabet Mellitus, Hemofili A, Hepatit B virüsü, Hepatit C virüsü, Hipertansiyon, Obezite

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INTRODUCTION

Hemophilia A is a congenital X-linked hemostatic disorder due to Factor VIII deficiency. Patients were generally diagnosed during early childhood. Owing to the improvements in the medical management of bleeding episodes, those patients usually are reached adulthood and life expectancy had increased dramatically. Chronic age related medical problems may be observed in these patients (1-4). Those chronic conditions may be overlooked by the clinicians and likewise patients may not be concerned sufficiently about their medical conditions other than hemophilia A. Also, adult patients with hemophilia A are generally previously plasma treated patients in whom blood-borne viral infections can be seen as complication (5). In this study we aimed to investigate comorbidities and transfusion transmitted infections observed in the adult hemophilia A patients in our tertiary center.

METHODS

Patient population

Adult hemophilia A patients in Hacettepe University Faculty of Medicine Department of Hematology were reviewed retrospectively for analysis Patients were diagnosed between the years of 1961 and 2007.

Data collection

Demographic data, plasma exposures, factor VIII administration histories, comorbidities, body mass indexes and markers for Hepatitis B virus (HBV), Hepatitis C virus (HCV) and Human Immunodeficiency virus (HIV) infection were recorded.

Statistical analysis

Univariate analyses were performed via Chi-square test for categorical and by t-test for numerical variables, respectively. Multivariate analyses were performed by Cox regression analysis.

Ethics

This study was conducted according to the Helsinki Declaration, and the study protocol was approved by the local institute's Committee on Research (our local ethics body; 03.2018; 18/163 approval number).

RESULTS

A total of 26 patients were in strict follow up in our Hemophilia A cohort. Median age was 44 (21-59), all male. Median time from diagnosis to last visit was 40 years. 2 patients were diagnosed at adulthood. Patients with mild hemophilia (Factor VIII activity > 5%), moderate hemophilia (Factor VIII activity 1-5%) and severe hemophilia (Factor VIII <1%) with and without FVIII inhibitors were represented in Table 1.

Four (15%) patients had inhibitors at last visit. Patients had no history of recent immunization at last visit. Two more patients had inhibitor titer more than 0.6 Bethesda Units during follow-up which became negative at subsequent visits.

Bleeding characteristics of patients

Twelve patients had more than 3 annual bleeding episode and 5 of those were bleeding more than 10 per year. Ten patients had never experienced severe life-threatening bleeding. Severe bleedings are represented in Table 2.

Table 1. Characteristics of Hemophilia A patients

	No Inhibitor	Low-titer inhibitor (<5 BU/ml)	High-titer inhibitor (≥5 BU/ml)
Mild hemophilia (n=6)	6	0	0
Moderate hemophilia (n=6)	4	0	2
Severe hemophilia (n=18)	16	0	2

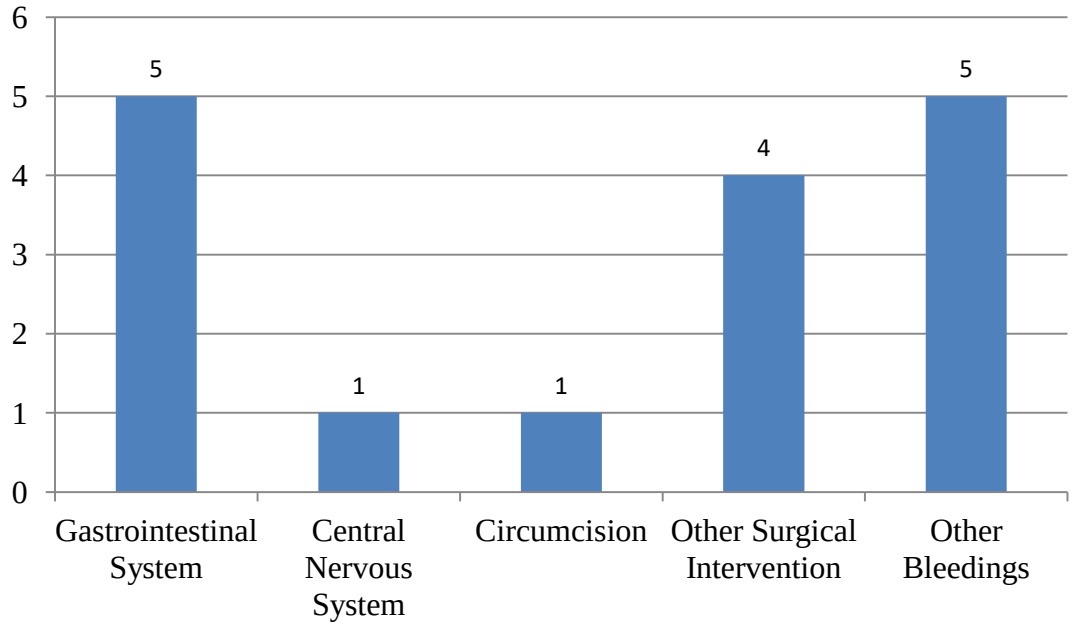

Table 2. Life threatening bleedings of Hemophilia A patients

Factor replacement habits

Median age at first factor replacement was 1.5 (0-40). Twenty-three (88%) of patients were previously treated with fresh frozen plasma. Twelve (46%) were currently using plasma derived factor VIII products and 10 were using recombinant factor VIII products (7 cases second generation and 3 cases third generation).

Four (15%) patients had inhibitors and were currently using bypassing agents. One patient with moderate hemophilia with high annual bleeding rate was using concizumab in addition to third generation recombinant factor VIII product. Antifibrinolytic usage was uncommon; only two patients were using it as an adjunct to factor replacement.

Twenty-four patients were applying factor product as home-therapy, 2 of them by help of a nurse and remaining by self-injection. Fourteen patients were treated with factor replacement on demand, remaining were using prophylaxis, one with inhibitors. Patients in prophylaxis had severe hemophilia A except one patient, who had admitted to our clinic from a different center while using prophylaxis.

Comorbidities

Common comorbidities are listed in Figure 1. Median age was significantly different between diabetic and non-diabetic patients (p=0.040). At last visit, 3 patients had high blood pressure measurements and were advised to monitor their blood pressures, 1patient also had high fasting glucose (>126 mg/dL) and high fasting triglyceride (>500 mg/dL) discovered incidentally. Anemia was seen in 4 patients, one was associated with iron deficiency and others were not evaluated. There were no patients with chronic liver or renal failure.

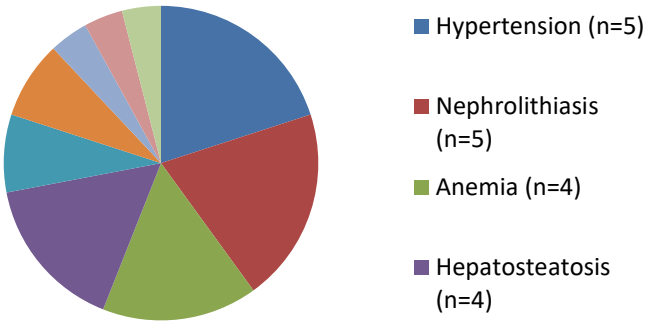

Figure 1. Common comorbidities in Hemophilia A patients

Median body mass index (BMI) was 27 kg/m^2. Of whom body mass index was known, 25% were obese and 70% were overweight and/or obese. Being overweight and obese (BMI≥25 kg/m^2) is not found as a risk factor for DM (p=0.507), HT (p=1.000) and for hepatosteatosis (p=1.000). Being obese (BMI≥30 kg/m^2) is also not found as a risk factor for DM (p=1.000), HT (p=0.280) and for hepatosteatosis (p=0.546).

Transfusion-transmitted infections

HBV serology was unchecked in 6 patients. Of 20 patients with checked HBsAg, 2 had positive HBsAg and HBV PCR. Eight cases had negative HBsAg with antiHBc total positivity (checked in 13 cases); 5 of them had negative HBV DNA (accepted as occult hepatitis) and 3 had unchecked HBV DNA. Three cases were accepted immunized to HBV and remaining had not sufficient test to give a diagnosis. Nineteen (73%) had serum anti-HIV checked and all were negative.

Six of 19 patients (32%) in whom anti-HCV checked, had anti-HCV positivity and 2 of them had positive viral load. A total of 8 patients had liver function test abnormalities; 2 were HCV RNA positive, 3 had exposed to either HBV or HCV and 2 had no viral serology or molecular tests. None of the patients had chronic hepatitis failure but 4 patients had hepatosteatosis, 1 of them had HBV PCR positivity. Only 1 patient was currently using antiviral treatment for his HBV but he was incompliant with his treatment.

DISCUSSION

Severe bleeding has become a less occurring event in Hemophilia A since the advent of factor concentrates in 1970s(1). Blood-borne infections emerged with early plasma derived factor VIII preparations (4, 6) but highly active antiretroviral therapy and other antiviral drugs also prolonged the life expectancy of patients with hemophilia infected with HIV and hepatitis viruses(1, 4). Increased life expectancy has brought along with chronic medical conditions like hypertension, diabetes(1, 2). It is unclear that whether hemophilia protects from atherosclerosis due to hypocoagulability in its nature (1, 3), authors conclude that the risk of death due to cardiovascular disease may be lower in patients with hemophilia (2). In an excellent rewiew Shapiro emphasizes that atherosclerosis was similar between patients with and without hemophilia. But patients without hemophilia tend to have higher cardiovascular mortality(4). Situations indicating antiagregation and/or anticoagulation may put the clinicians in a troubled condition dealing with congenital factor deficiencies and there are no guidelines with firm evidences for management of those patients.

In our study there were patients with diabetes and/or hypertension. According to Patent2 study, hypertension prevalence in males aged 40-49 (matching our study group) is 26.9% and awareness of hypertension in males is 40.6% for all age groups(7). Hypertension was seen less in our hemophilia cohort (19%) but the results of an Italian survey of men aged 65-78 years in 2009, revealed that hypertension prevalence was significantly higher in hemophilia than in the general population (8). In 2013 in a study of von Drygalski this higher hypertension prevelance was also shown and blood pressure control was also lower than the general population (9). Recent Swedish registry data also showed compatible results (10). In a Japanese data; hypertension prevalence was not high in patients with hemophilia with same blood pressure definitions of Patent2 (11). In our hemophilia cohort there were 3 patients unaware of their high blood pressure but we don't know whether they have white coat hypertension.

Known diabetes prevalence of urban males aged 40-44 in Turkey is 7.3% according to TURDEP-II Study Group data(12). Diabetes was similar (7.6%) in our hemophilia cohort with unknown reasons. In our hemophilia cohort there were patients unaware of their high fasting blood sugar and fasting lipids also.

Although factor concentrate replacement decreases bleeding and related complications, arthropathy is still a serious health problem in adult Hemophilia A population. Those patients reached adulthood with arthropathy before the advent and widespread use of factor concentrates(1, 3). In this study we did not mention here the arthropathy scores of our Hemophilia A cohort. But obesity which may worsen joint problems in hemophilia A is analyzed. Median body mass index and the percentage of overweight and/or obese patients show that obesity and/or being overweight is not a negligible problem in our hemophilia A cohort. According to the detailed literature search and meta-analysis of Wilding et al, the estimated pooled prevalence of overweight/obesity in European and North American patients with hemophilia was 31% (13). Although few studies have assessed the effects of obesity on hemophilia-specific outcomes, Kahan et al reviewed literature published over the past 15 years and discussed implementing general guidelines for weight management(14).

Chronic kidney disease is also reported to be higher in the hemophilia population compared to the general population, most probably due to higher rate of hypertension, genitourinary bleedings, HIV infection (1, 2, 4). Nephrolithiasis is also a risk factor for chronic kidney disease (3). Nephrolithiasis was seen in 5 cases in our cohort; but data in literature about mechanisms and management is scarce. There were no cases with acute kidney failure but risk is higher in patients with hemophilia according to previous reports (4).

HCV is defined as a major cause of mortality and morbidity in hemophilia (15, 16) sometimes co-infections may be seen with HBV and HIV (15, 17). Anti-HCV positivity in hemophilia is different between different study groups(5, 18). Eighty percent of the subjects develop chronic hepatitis C infection (17, 19). There were no cases with HIV in our cohort, which may be a cardiovascular risk factor due to several reasons beyond other problems attributed to immune deficiency (3).The results of our present study revealed that HBV and HCV exposure is common in patients with adult hemophilia A in whom plasma exposure frequency is high. There were cases that viral serology has never been checked. The diagnostics for transfusion transmitted infections seem not to be given enough importance in this cohort. Treatments for these viruses and follow-up of infections are beyond the scope of this study.

High prevalence of unawareness of chronic medical conditions in general population may be due to several reasons but we think that in hemophilia, cases may be overwhelmed with frequent hospital visits for bleeding and factor prescriptions. Debilitations caused by arthropathy may also result in less utilization of other health sources like general practitioners. We suggest that hemophilia cases should be monitored for chronic health conditions during hematology visits. Body mass index, blood pressures, fasting lipids and glucose should be checked. Healthy weight loss should be recommended for every patient with hemophilia. Diet for comorbidities and appropriate exercise program should be incorporated into hemophilia management. Clinicians should be aware of blood-borne pathogens and they should perform screening tests for those received fresh frozen plasma.

Standards for comprehensive care for hemophilia and other inherited bleeding disorders were reviewed very recently (20) and we think that there should be standards of comprehensive care for hemophilia A implemented in routine daily practice in every hemophilia treatment center.

Conflict of interest

No conflict of interest was declared by the authors.

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