

Multimorbidities and polypharmacy in ageing hemophilia patients

Yaşlanan hemofili hastalarında multimorbiditeler ve çoklu ilaç kullanımı

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ABSTRACT

Aim: The aim of the study was to investigate whether multimorbidities, comorbidities, and therefore polypharmacy increase with age in hemophilia A and B patients followed in Ege University Adult Hemophilia and Thrombosis Center.

Materials and Methods: Adult hemophilia A and B patients were retrospectively evaluated. Patients' demographic data, medical information about hemophilic arthropathy, viral infections hepatitis C virus (HCV), body mass index (BMI), smoking and alcohol consumption, concomitant diseases, and all medications except factor replacement therapy were analyzed. Polypharmacy was defined as ≥ 5 drug use. Patients were compared by dividing into two groups: ≤ 55 years and > 55 years.

Results: A total of 230 patients were evaluated (189 hemophilia A, 41 hemophilia B). There were 191 patients in ≤ 55 years (83%), and 39 patients in > 55 years age groups (17%). The most common diseases in hemophilia patients were hypertension (19.5%), diabetes mellitus (10%), and gastroesophageal reflux disease-chronic gastritis (5.2%). The most common drugs that patients use regularly were non-steroidal anti-inflammatory drugs (14.3%), proton pump inhibitors (12.1%), and oral antidiabetics (9.5%). The number of diseases not related to hemophilia (multimorbidity) and polypharmacy in hemophilia patients aged > 55 years was significantly higher than those aged < 55 years (p values were 0.00 and 0.01 respectively). There was no difference between the groups in BMI, alcohol and cigarette use, and the history of HCV infection.

Conclusion: Our study showed that aging hemophilia patients have more multimorbidities and use more drugs than younger patients. For this reason, the importance of the effects of additional diseases and drugs on quality of life, treatment compliance, and hemostasis is increasing.

Keywords: Hemophilia, polypharmacy, multimorbidity.

ÖZ

Amaç: Çalışmamızın amacı Ege Üniversitesi Erişkin Hemofili ve Tromboz Merkezi'nde takip edilen hemofili A ve B hastalarında yaşla birlikte multimorbidite, komorbidite ve dolayısıyla polifarmasi artışı olup olmadığını araştırmaktır.

Gereç ve Yöntem: Takip edilen erişkin hemofili A ve B hastaları geriye dönük olarak değerlendirildi. Hastaların demografik verileri, hemofilik artropati, hepatit C virüsü (HCV) ile ilgili tıbbi bilgileri, vücut kitle indeksi (VKİ), sigara ve alkol kullanımı, eşlik eden hastalıkları ve faktör replasman tedavisi dışındaki tüm ilaçları incelendi. Polifarmasi, ≥ 5 ilaç kullanımı olarak tanımlandı. Hastalar ≤ 55 yaş ve > 55 yaş olarak iki gruba ayrılarak karşılaştırıldı.

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Application date: 18.03.2022 Accepted: 14.09.2022

Bulgular: Toplam 230 hasta değerlendirildi (189 hemofili A, 41 hemofili B). ≤55 yaş grubunda (%83) 191 hasta ve >55 yaş grubunda (%17) 39 hasta vardı. Hemofili hastalarında en sık görülen hastalıklar hipertansiyon (%19,5), diabetes mellitus (%10) ve gastroözofageal reflü hastalığı-kronik gastrit (%5,2) idi. Hastaların en sık kullandıkları ilaçlar nonsteroid antiinflamatuar ilaçlar (%14,3), proton pompa inhibitörleri (%12,1) ve oral antidiyabetiklerdi (%9,5). 55 yaş üzeri hastalarda hemofili ile ilişkili olmayan hastalıklar (multimorbidite) ve polifarmasi <55 yaş grubuna göre anlamlı olarak daha fazlaydı (sırasıyla p değerleri 0.00 ve 0.01). Gruplar arasında VKİ, alkol ve sigara kullanımı ve HCV enfeksiyon öyküsü açısından fark yoktu.

Sonuç: Çalışmamız, yaşlanan hemofili hastalarının genç hastalara göre daha fazla multimorbiditeye sahip olduğunu ve daha fazla ilaç kullandığını göstermiştir. Bu nedenle ek hastalık ve ilaçların yaşam kalitesi, tedaviye uyum ve hemostaz üzerindeki etkilerinin önemi giderek artmaktadır.

Anahtar Sözcükler: Hemofili, polifarmasi, multimorbidite.

INTRODUCTION

In recent years, the life expectancy and health-related quality of life hemophilia patients have increased significantly with the developments in factor replacement therapies and advances in patient care. Thus, the number of patients who reach advanced ages and meet the problems brought about by aging has also increased. The societal consequence of this situation is that there is a much older population of hemophiliacs than in previous generations. Such a condition brings along especially cardiovascular and malignant diseases, liver diseases, bone and joint-related diseases, dementia, obesity, and decreased physical ability, lifestyle problems, sexual disorders, depression, and psycho-social problems (1). Healthcare professionals serving these individuals are faced with both hemophilia-related comorbidities and aging-related multimorbidities (2, 3). Comorbidity is defined as the disease associated with the primary disease of the individual, while multimorbidity is defined as the chronic coexistence of more than two conditions unrelated to the primary disease (4). According to this definition, comorbidities associated with hemophilia are arthropathy, myopathy, viral infections, and osteoporosis, while multimorbidities in aging hemophilia individuals are diseases such as liver and kidney diseases, cancer, and cognitive disorders (2). As the concomitant disease/condition increases, the number of drugs used also increases. The generally accepted definition of polypharmacy is the chronic concomitant use of 5 or more drugs (5). Polypharmacy has some adverse effects, especially in hemophilia patients (6): tendency to bleeding, treatment non-compliance, increase in drug side effects (7), inappropriate drug use, drug-drug interactions, impaired functional status (8), increase in health expenditures (9), and improper prescribing-deprescribing (10). The

issue becomes even more important today as the aging population of hemophilia and therefore age-related problems and polypharmacy increase. The aim of our study was to evaluate if co- and multimorbidities, and therefore polypharmacy, increase with age in patients with hemophilia A and B followed-up at the Ege University Adult Hemophilia and Thrombosis Center.

MATERIALS and METHODS

This study was a single-center, and retrospective cohort study. Adult hemophilia A and B patients followed by Ege University Adult Hemophilia and Thrombosis Center between 2000 and 2021 were retrospectively evaluated. We obtained ethical approval from the local Ethics Committee. Their demographic data and medical records regarding hemophilic arthropathy, hepatitis C virus (HCV) infection, body mass index (BMI), smoking, alcohol consumption, concomitant diseases, and all medications except factor replacement therapy were recorded. Polypharmacy was defined as ≥5 drug use. Patients were divided into two groups as ≤55 years and >55 years and compared. Data were reported as frequency (percentage) or median for categorical and continuous variables. IBM SPSS Statistics 25 for Windows was used for statistical analyses. The characteristics of these two age groups were compared with the T-test. p value less than 0.05 was accepted as statistically significant.

RESULTS

A total of 230 patients were evaluated (189 hemophilia A, 41 hemophilia B). Due to the nature of the disease all patients were male. At the time of data collection, mean age of the study group was 40.79 years (18.7-71.8). There were 191 patients in ≤55 years (83%), and 39 patients in >55 years age groups (17%). The distribution according to the severity of hemophilia is as

follows: 135 severe (59%), 56 moderate (24%), and 39 (17%) patients had mild hemophilia. Mean BMI was 25.7 kg/m² (16.3-43.6). One hundred and fifty-six patients (68%) were receiving prophylaxis, and 74 patients (32%) were on-demand treatment. Fifty one patients had no hemophilic arthropathy (22%). None of the patients had active HCV infection. Clinical characteristics of the patients were summarized in Table-1. The number of diseases not related to

hemophilia (multimorbidity) and polypharmacy in hemophilia patients aged >55 years was significantly higher than those aged <55 years (*p values were 0.00 and 0.01* respectively). There was no difference between the groups in BMI, alcohol and cigarette use, and the history of HCV infection.

The most common diseases are listed in Table-2. The drugs that used regularly by the patients are listed in Table-3.

Table-1. Clinical characteristics.

	Total		≤55 years		>55 years		p value
	N:	%	N:	%	N:	%	
Alcohol							
Yes	72	31.3	58	30.4	14	35.9	0.49
No	158	68.7	133	69.6	25	64.1	
Smoking							
Yes	114	%49.5	95	49.7	19	48.7	0.9
No	116	%50.5	96	50.3	20	51.3	
BMI ≥25	25.7		25.7		26.1		0.4
Past HCV infection	37	%16	31	%16.2	6	%15.4	0.8
Multimorbidity	0.62		0.43		1.51		0.00
Polipharmacy	21	%9	8	%4.2	13	%33.3	0.01

BMI: Body mass index, HCV: Hepatitis C virus

Table-2. Other diseases in Haemophilia A and B patients.

Disease	Number (%)
Hypertension	45 (19.5%)
Diabetes mellitus	23 (10%)
Gastroesophageal reflux disease, chronic gastritis	12 (5.2%)
Coronary artery disease	7 (3%)
Depressive disorders	7 (3%)
Dyslipidemia	6 (2.6%)
Epilepsy	6 (2.6%)
Hypothyroidism	5 (2.1%)
Asthma	4 (1.7%)
Chronic kidney disease	3 (1.3%)
Arrhythmia	2 (0.8%)
Benign prostate hyperplasia	2 (0.8%)
Chronic obstructive pulmonary disease	2 (0.8%)
Inflammatory arthritis	2 (0.8%)
Allergic rhinitis	2 (0.8%)
Glaucoma	2 (0.8%)
Buerger disease	1 (0.4%)
Irritable bowel syndrome	1 (0.4%)
Hyperparathyroidism	1 (0.4%)
Chronic pancreatitis	1 (0.4%)
Cataract	1 (0.4%)

Table-3. Drugs that patients use regularly.

Drug name	Number of patients	%
Non-steroidal anti-inflammatory drug	33	14.3
Proton pump inhibitor	28	12.1
Oral antidiabetic	22	9.5
Beta blocker	18	7.8
Angiotensin receptor blocker±diuretic	17	7.3
Paracetamol	16	6.9
Angiotensin converting enzyme inhibitor±diuretic	15	6.5
Anti-lipidemic (statin+fibrat)	10	4.3
Calcium channel blocker	9	3.9
Antiepileptic	8	3.4
Antidepressant	8	3.4
Acetylsalicylic acid	6	2.6
Antihistaminic	6	2.6
Insulin	6	2.6
Antianginal	5	2.1
Inhaler	5	2.1
Antiarrhythmic	4	1.7
Thyroid hormone replacement	4	1.7
Leukotriene antagonist	3	1.3
5 alpha reductase inhibitor	3	1.3
Antacid	3	1.3
Pancreas hormone extract	2	0.8
Clopidogrel	2	0.8
Ursodeoxycholic acid	2	0.8
Diuretic	2	0.8
Tranexamic acid	2	0.8
Erythropoietin	1	0.4
Gabapentin	1	0.4
Methotrexate	1	0.4
Hydroxychloroquine	1	0.4
Steroid (oral)	1	0.4
Alfa blocker	1	0.4
Antiviral (HBV)	1	0.4
Muscle relaxants	1	0.4

DISCUSSION

Although the number of studies about polypharmacy in hemophilia patients is not

sufficient yet, this issue is drawing attention and gaining importance day by day. Recently, in a study conducted with 102 patients over 60 years

of age with hemophilia, the patients were compared with the age- and residence-matched control group in terms of polypharmacy. In the comparison made by excluding replacement therapies and antiviral drugs, it was reported that patients with hemophilia used less daily medication compared to the control group and therefore experienced less drug-drug interactions. The authors attribute this to the careful prescribing approach in specialized hemophilia centers and the relatively younger 'elderly' study group. In the study, it was also determined that patients with hemophilia used anti-acids (especially proton pump inhibitors), cardiac drugs, urological drugs, anti-inflammatory drugs, and anti-rheumatic drugs more than those without hemophilia (11). Although our study is not comparing individuals with and without hemophilia, the most frequently used drugs in our patient group are similar.

In a single-center Italian study consisting of one hundred and thirty-five hemophilia patients, the patients were divided into two groups as over 55 and under. Polypharmacy (5 or more drugs) in elderly patients was significantly higher than in younger patients (27% vs 16%, $p=.001$). While the mean number of drugs used in the elderly group was 3.4 ± 2.29 , this number was 2.6 ± 1.8 in young people ($p=.03$). In addition, it was observed that the elderly group used more antihypertensive drugs, vitamins, proton pump inhibitors, and less anti-inflammatory drugs and topical pain relievers (for the musculoskeletal system) compared to the younger group. Researchers stated that they encountered less drug use than they expected in elderly hemophilia patients. Like in the other study previously mentioned, they suggested that the patients had close and regular follow-up in specialized hemophilia centers as the reason for this (2). Although there were no significant differences in median or mean patient ages (mean age 47.7 years in Italian group and median age was 40.79 in our group) and frequency of patients over 55 years of age between the two studies (27.4% vs 17%), the difference in the frequency of polypharmacy between the group of patients over and under 55 years of age was found to be significantly higher in our study (4.2% vs 33.3%).

Although not directly related to polypharmacy, the American Thrombosis and Hemostasis Network compared 200 hemophilia patients with a mean age of 61 years with age-matched controls from

two large studies (ARIC and NHANES). As this study is associated with cardiovascular diseases, the analysis is also on drugs in this area. It has been found that patients with hemophilia use antihypertensive, lipid and glucose-lowering drugs, especially aspirin, at a lower rate (12). Although the frequency of diabetes mellitus and hypertension was similar to our study, dyslipidemia was found to be significantly higher in this study (63.5% vs 2.6%). Since the use of acetylsalicylic acid in this study was indicated only in patients with cardiovascular disease (10%), it would not be correct to compare it with the general rate in our study (2.6%).

Being aware of the problems that hemophilia patients may encounter with the use of multiple drugs is the first and basic precaution that can be taken. With a detailed and holistic evaluation performed in specialized hemophilia centers, the functional characteristics, mood, cognitive capacity and current drug use of the patient should be questioned. In addition, close communication with other branches such as internal medicine, geriatrics and clinical pharmacology will be beneficial for patient management. Special care should be taken when selecting drugs that should be personalized according to the patient's age, functional status, co- and multi-morbidities, and most importantly, impaired hemostasis. In addition to the aforementioned subspecialties, hemophilia nurses have a major role in the management, coordination and follow-up of aging hemophilia patients (2).

In our opinion it is not suitable or sufficient to comply with standard recommendations and general guidelines in the management of multiple and comorbidities in patients with hemophilia. For the general population, the management of most age-related diseases is based on observational and interventional studies. For example, drugs recommended for use in the general population, such as anti-thrombotic agents in such studies, may not be appropriate in patients with bleeding disorders because they affect hemostasis. It is not always easy to conduct the large-scale studies needed to clarify treatment in the relatively small number of hemophiliacs. In such cases, information obtained from expert opinions and observational study data gain importance (1). Currently, the general information is that elderly hemophiliacs should be treated like their non-hemophiliac peers as long as factor replacement is performed (13).

CONCLUSION

Our study showed that polypharmacy and multimorbidities increase by age in hemophilia patients. For this reason, there is a need to collect and learn more information about the polypharmacy faced by elderly and multi-morbid hemophilia patients and the effect of these drugs on the patient's general condition and bleeding susceptibility. Moreover, health care professionals dealing with a rare disease such as

hemophilia should be informed and appropriately trained about this increasing problem in aging patients to update and optimize the interdisciplinary approach required in the management of complex and chronic elderly patients using multiple medications (14).

Conflict of interest: The authors declare that they do not have any conflict of interest. This research did not receive any funding.

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