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Original Article

Hematuria in Patients with Congenital Coagulation Factor Deficiencies

Konjenital Kanama Bozukluklarında Hematüri

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ABSTRACT

Objective: Inherited bleeding disorders are a group of congenital coagulopathies, arising due to protein deficiencies, which affect clotting, platelet function or fibrinolysis. Spontaneous gross hematuria or subclinical microscopic hematuria, which are often detected by chance, are relatively common in patients with coagulopathies. This study aims to evaluate the incidence, the causes and treatment modalities of hematuria in congenital factor deficiencies.

Method: Data concerning the type of coagulation defect, the level of deficient factor, age of the patients with hematuria episodes, presence of inhibitor, ongoing treatment modality, the etiology of hematuria, the treatment approach to hematuria, the number of hematuria episodes has been collected from medical records and hemophilia dairies of patients between 1985 and 2015 and confirmed by phone calls. Six hundred twenty nine patients with congenital factor deficiencies followed were evaluated retrospectively.

Results: Hematuria was seen in 10.1% of hemophilia A, 15.5% of hemophilia B, 3.8% of von Willebrand's disease patients and 7% of patients with other factor deficiencies. Hematuria was seen in 2 mild, 20 moderate and 29 severe factor VIII and IX deficiencies. In 7 of these patients inhibitor was positive. While no etiological reason for hematuria could be identified in 78% of these patients, 15.3% had nephrolithiasis, 1.7% had post streptococcal acute glomerulonephritis, 3.4% had urinary tract infection and 1.7% had a renal cyst.

Conclusion: The study demonstrates that hematuria is relatively common in factor deficiencies, whereas further studies are needed to elucidate the causes and effects on renal function in children with coagulation deficiencies.

Keywords: Macroscopic hematuria, congenital coagulation deficiencies, hemophilia

ÖZ

Amaç: Kalıtsal kanama bozuklukları, pıhtılaşmayı, trombosit fonksiyonunu veya fibrinolizi etkileyen protein eksiklikleri nedeniyle ortaya çıkan bir grup hastalıktır. Genellikle tesadüfen saptanan spontan gros hematüri veya subklinik mikroskobik hematüri nispeten yaygındır. Bu çalışmada kanama bozukluklarında hematürinin görülme sıklığı, nedenleri ve tedavi yöntemlerinin değerlendirilmesi amaçlanmıştır.

Yöntem: Kalıtsal kanama bozukluğu tanısı ile takip edilen 629 hastanın retrospektif olarak değerlendirildi. 1985 ve 2015 yılları arasındaki hastaların tıbbi kayıtları ve hemofili günlükleri ve telefon görüşmeleri ile teyit edildi. Pıhtılaşma bozukluğunun tipi, eksik faktör düzeyi, hematüri atakları olan hastaların yaşı, inhibitör varlığı, devam eden tedavi şekli, hematürinin etiyolojisi, hematüriye tedavi yaklaşımı, hematüri atak sayısı incelendi.

Bulgular: Hematüri, hemofili A'nın %10,2'sinde, hemofili B'nin %15.6'sında, von Willebrand hastalığı olan hastaların %3,9'unda ve diğer faktör eksikliği olan hastaların %7,5'inde görüldü. Yirmi dokuz şiddetli, 20 orta ve 2 hafif faktör VIII ve IX eksikliğinde hematüri görüldü. Bu hastaların 7'sinde inhibitör pozitifti. Bu hastaların %78'inde hematüri için herhangi bir etiyolojik neden saptanamazken, %15,3'ünde nefrolitiazis, %1,7'sinde streptokok sonrası akut glomerülonefrit, %3,4'ünde idrar yolu enfeksiyonu ve %1,7'sinde böbrek kisti vardı.

Sonuç: Çalışma, faktör eksikliklerinde hematürinin nispeten yaygın olduğunu gösterirken, pıhtılaşma eksikliği olan çocuklarda böbrek fonksiyonu üzerindeki nedenleri ve etkileri aydınlatmak için daha fazla çalışmaya ihtiyaç vardır.

Anahtar kelimeler: Makroskobik hematüri, konjenital koagülasyon defekti, hemofili

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INTRODUCTION

Inherited bleeding disorders are a group of congenital coagulopathies which occur as a result of protein deficiencies, which affect clotting, platelet function or fibrinolysis.

Hemophilia A (HA), hemophilia B (HB), von Willebrand's disease (VWD) and other rare congenital coagulation deficiencies (factor V, VII, V+VIII, X, XI deficiencies, etc.) are the most frequently seen inherited bleeding disorders in the general population, varying between 1 in 10.000 to 1 in 2 million [1-5].

Spontaneous gross hematuria or subclinical microscopic hematuria, which is often detected incidentally, is relatively common in patients with hemophilia. In two studies of hemophiliacs, 66% of the patients had a history of hematuria [6,7]. Hematuria is usually considered to be in benign nature, unless accompanied by ureteral clots. Hematuria can have several causes including history of analgesics (anti-inflammatory drugs), calcium and vitamin D intake, stress, trauma, and exercise [8,9]. The etiology of spontaneous hematuria is not known.

This study retrospectively evaluates the incidence and causes of macroscopic hematuria in patients with hemophilia and the other bleeding disorders and the general approach to hematuria in our clinic.

MATERIALS and METHODS

Six hundred twenty nine patients with congenital factor deficiencies, who were being followed up in a tertiary university hospital, were retrospectively searched for reported macroscopic hematuria episodes. Data from the period 1985 to 2020 was collected from medical records and hemophilia dairies of patients and confirmed by phone calls. The name of the coagulation deficiency, the deficient factor level, presence of inhibitor, gender, age, the history of bleedings, the examinations to rule out the etiologies of hematuria, the reasons of bleedings, the ongoing treatment and the medical approach to bleedings were noted from the medical records. Although urine analysis had been performed to all patients with hematuria, urine culture had been performed only for ten patients. Abdominal ultrasonography was performed on 52 patients and further investigations were done according to the history and physical examination in few patients. Within the scope of this study, the age of the patients with hematuria, the etiology of hematuria, the treatment approach to hematuria, the numbers of hematuria episodes were collected.

The study was approved by Ege University Faculty of Medicine Medical Research Ethics Committee (decision number: 21-5T/118, date: 20.05.2021).

The severity of hemophilia was categorized as severe if the baseline clotting FVIII or FIX activity was ≤1%, moderate if >1-5% and mild if >5-30% [9]. The type of VWD was categorized according to International Society of Thrombosis and Hemostasis-Scientific and Standardization Committee [10]. The inhibitor titer was measured at least once-a-year and viral serology was tested routinely once a year.

Statistical Analysis

The data analyzed using SPSS (Statistical Package for Social Sciences) statistical program (version 17.0). Mean values and standard deviation were calculated for continuous variables. Categorical variables were compared by using chi-square test. Since the groups were not normally distributed, Mann-Whitney U test was applied to make a comparison in terms of hematuria frequency and incidence between severe, moderate and mild deficiencies and between inhibitory positive and negative hemophilia. The differences between HA, HB and VWD were analyzed using Kruskal-Wallis variance analysis and the findings were considered as significant when the case was $p<0.05$.

RESULTS

A total of 629 [mean age: 17.1±14.7 (1-45) years, 549 (87%) of them males, mean follow-up time: 16.1±11.7 years] medical records, consisting of 383 (60.9 %) HA [185 (48.3%) severe; 56 (14.7%) moderate; 142 (37%) mild HA], 77 (12.2%) HB [52 (67.5%) severe; 15 (19.5%) moderate; 10 (13%) mild HB], 99 (15.7%) type-1, 16 (2.5%) type-2 and 14 (2.2%) type-3 VWD, 16 (2.5%) FVII deficiency, 8 (1.3%) FV deficiency, 5 (0.8%) FX deficiency and 11 (1.7%) other rare factor deficiencies were examined. Thirty four of the patients with hemophilia (31 HA and 3 HB) had inhibitory.

Macroscopic hematuria was seen in 59 (9.4%) of 629 patients with coagulation deficiencies. Hematuria was seen in 39 (10.2%) of 383 HA patients, 12 (15.6%) of 77 HB patients, 5 (3.9%) of 129 VWD patients, 3 (7.5%) of 40 patients with other factor deficiencies (Table 1). There was no significant difference in terms of hematuria incidence between HA and HB ($p=0.207$). The VWD patients had a significantly lower hematuria incidence compared to

HA and HB patients (p=0.002). The mean age of the first hematuria attack was 15.5±6.9 (3-34) years.

While 34 patients had only one hematuria episode, 8 patients had two episodes, 4 patients had 3 episodes, 3 patients had four episodes and 10 patients had five and more episodes. None of the patients had history of trauma. Hematuria incidence was higher in patients with moderate and severe (15.9%, 49/308), compared to mild (1.9%, 3/155) factor VIII and IX deficiencies (p=0.012). Inhibitory was positive in 7 of these patients (6 HA and 1 HB). The number of bleeding episodes was not significantly higher in patients with inhibitor compared to patients without inhibitor (p>0.782).

Although there was no significant correlation between hematuria frequency and the factor levels (r=0.27, p>0.645), the hematuria incidence was significantly higher in severe and moderate hemophilia patients compared to mild hemophilia patients (p=0.01).

The ages of the patients with hematuria were between 3 and 34 years, with a mean age of 15 years. All of the patients with hematuria were above five years old except a three-year old female, who had hematuria because of a urinary tract infection, and a 4-year old male, who had hematuria because of nephrolithiasis.

In most of the bleeding episodes, patients didn't report pain, except nine patients with nephrolithiasis. Ultrasonography was performed on 52 of 59 patents with hematuria. While nephrolithiasis was seen in 9 patients (15.3%), pyelocaliectasis was seen in 1 patient (1.7%) and 1x1cm sized renal cyst in the upper renal parenchyma was seen in 1 patient (1.7%), all with hematuria, and no significant findings were observed in ultrasonography in 41 of 52 patients (78.8%). The stone was located either in renal pelvis or in ureter and none of them exceeded 1 cm diameter and no obstruction was seen in any of the patients with nephrolithiasis.

No reason could be identified in 46 (78%) of these patients.

While nine (15.3%) patients had nephrolithiasis (8 patients with HA/HB, 1 patient with VWD), 1 (1.7%) patient had pyelocaliectasis, 1 (1.7%) patient had post-streptococcal acute glomerulonephritis (PSAGN), 1 (3.4%) patient had a upper urinary tract infection, 1 (1.7%) patient had a renal cyst. Only 1 patient with hematuria had chronic hepatitis C (HCV) infection, and no other viral infection such as hepatitis B or human immunodeficiency virus (HIV) was found.

Regular screening tests such as urine analysis and ultrasonography were not applied in the follow ups.

As HA and HB are X-linked disorders of the coagulation system and the other coagulopathies incidences were lower, hematuria was seen in only 4 girls. Among these 4 female patients; one had factor V deficiency, one had factor VII deficiency and 2 had VWD. While one VWD patient with PSAGN and the other VWD patient with upper urinary tract infection were treated according to the treatment protocols of the diseases, the other two female patients (1 FVII deficiency with renal cyst and FV deficiency), who had severe factor deficiencies, were given hydration and factor replacement therapies.

Four of our patients were diagnosed with congenital coagulation deficiency when the cause of hematuria was being investigated (1 VWD and 3 hemophilia patients).

While eight (13.6%) patients were given only hydration therapy; forty three (72.9%) patients were given both hydration and factor replacement therapy at home (1-2 times factor replacement therapy). Five (8.5%) patients were hospitalized and received hydration and factor replacement therapy not more than three times. Since obtaining the factor was difficult because of the insurance policy of the country on supply of factor derivatives before 1999, two (3.4%) patients had

Table 1. Number of patients with macroscopic hematuria according to disease group

Diagnosis	Number of patients	Percentage	Age	Gender	Number of hematuria	Hematuria percentage
Hemophilia A	383	60.9	1-42 y	383 boys	39	10.2
Hemophilia B	77	12.2	1-45 y	77 boys	12	15.6
VWD*	129	20.5	4-38 y	68 boys	5	3.9
Other rare factor D**	40	6.35	3-17 y	21 boys	3	7.5
Total	629	100	1-45 y	549 boys	59	9.4

*VWD: von Willebrand's disease type 1, 2 and 3, **Factor V, FVII, FV+VIII, FX, FXI, FXIII deficiencies

been given fresh frozen plasma and one (1.7%) patient had been given fresh frozen plasma and prednisolone therapy in early years.

DISCUSSION

Hematuria which is commonly divided into two groups, as macroscopic and microscopic hematuria, is defined as the abnormal presence of red blood cells in the urine. Macroscopic hematuria can be observed from as little as 1 mL of blood in 1 L of urine, therefore the color does not reflect the degree of blood loss [11,12].

Both macroscopic and microscopic types hematuria are common among patients with hemophilia. Incidence of hematuria in patients with hemophilia varies between 9.3% to 66% in the literature [6-8,13]. However its long-term effects on the kidney and renal functions are not well defined. Hematuria is often detected by chance in hemophilia patients. The history of analgesics (anti-inflammatory drugs), calcium and vitamin D intake, stress, trauma, exercise can cause hematuria [8,9]. The etiology of spontaneous hematuria is not known. It is thought to be a reflection of tubular damage caused by circulating immune complexes [11]. In addition, contrary to the general belief that renal disease is a rare complication of hemophilia, Kulkarni et al. [8] has found acute or chronic renal disease in 2.9% of hospitalized hemophilia patients. Kulkarni et al., [8] have investigated data collected from the medical records of 3422 males with hemophilia living in six the United States states between 1993 and 1998. They have examined associations of renal disease with demographic and clinical factors including age, race, hemophilia type and severity, hypertension, diabetes, history of recent renal bleeds, presence of an inhibitor, and infection with HCV or HIV. The study has revealed that HIV infection and hemophilia-related factors including inhibitors and kidney bleeds associated with renal disease in a group of males with hemophilia [8].

The development of asymptomatic gross or microscopic hematuria is relatively common in children. Although the incidence of asymptomatic gross hematuria is unknown, the prevalence of asymptomatic microscopic hematuria in school-age children has been estimated as 0.5% to 2.0% [12,14]. As hemophilia patients have a tendency to bleed, reported macroscopic and microscopic hematuria incidence is between 9% and 66% [6,9,13]. In our study, the hemophilic patients' macroscopic hematuria incidence was found to be 9.4% which is similar to a study which had been performed by Schlussel [15].

The most prominent symptom in VWD is mucosal bleeding (eg, epistaxis, gastrointestinal bleeding and menorrhagia) [16]. Incidence of hematuria has not been reported in the literature. In our study five (3.9%) of 129 VWD patients had a macroscopic hematuria episode. In VWD patients, the etiologies of the hematuria consist of urinary tract infection in one patient, nephrolithiasis in one patient and PSAGN in one patient. One of these patients received the diagnosis of VWD while he was being examined for hematuria.

Macroscopic hematuria has an estimated incidence of 1.3 per 1000 in the pediatric population [17]. Although hematuria origins from the lower urinary tract in most patients, in less than 10% of the cases, hematuria is caused by glomerular bleeding [18]. A clinician should ensure that while avoiding the unnecessary and expensive laboratory tests, serious conditions do not remain unnoticed and provide necessary advice for further evaluation wherever needed. Obtaining the true history of the condition and physical examination are the most important steps in the treatment of hematuria.

In our cohort, the hematuria episodes were seen at between 3 and 34 years of age, with a mean age of 15 years. All of the patients who had hematuria were above 5 years of age except a 3-year old female, who had hematuria because of urinary tract infection and a 4-year old male, who had hematuria because of nephrolithiasis. Hematuria episodes in hemophilia patients, according to the literature, developed after the age of 5 [19].

Among all hemophiliac patients whose medical records were examined, nephrolithiasis was seen in 1.4% of the patients. In general population under the age of 40, this ratio is 4.5/10.000. Nephrolithiasis frequency is much higher in hemophilic patients [20,21]. Ghosh et al., [20] have performed a retrospective study on 474 hemophiliacs aged between 1-64 years (only six of them was over forty years) with two or more episodes of hematuria. Nephrolithiasis had been determined in 1.3 % of the patients with moderate and severe hemophilia. In all these patients, the stone was either in renal pelvis or in the ureter. Also several genes linked to X chromosomes [21] may be responsible for abnormal vitamin D metabolism, and renal tubular acidosis may cause stone formation. One of the most important features in hemophiliacs in developing countries, is repeated joint bleeds that causes osteoporosis and increases calcium resorption of the bone and consequently, elevated calcium in the urine [20]. In line with the existing literature, no significant correlation between deficient factor levels

and hematuria frequency was found in our study [22,23]. But hematuria incidence was higher in patients with moderate and severe hemophilia compared to patients with mild hemophilia (p=0.01). However, the etiology of hematuria in hemophilia is often unclear, and it may be attributed to the underlying coagulation deficiency.

No other infectious agents were found in patients with hematuria. Viral infections may induce hematuria and renal disease in hemophilia patients [8], but the number of infected patients was relatively low in our patient group and incidence of hematuria among them was not significantly higher. Only one (1.7%) patient with hemophilia had chronic HCV infection.

Since the treatment options of hematuria patients with coagulation deficiencies couldn't be determined after such a long period of time we had excluded the treatment modalities.

Study Limitations

The limitations of our study are; first of all, it is a retrospective study, which was conducted by using the data collected from patient reports. Moreover, the effects of hematuria on kidney function were not assessed, regular screening tests such as urine analysis and ultrasonography were not applied in the follow ups and metabolic evaluation for nephrolithiasis is lacking.

CONCLUSION

The increased prevalence of macroscopic hematuria among children with congenital coagulation factor deficiencies is shown. Further studies will help to elucidate the causes and effects on renal function.

Ethics

Ethics Committee Approval: The study was approved by Ege University Faculty of Medicine Medical Research Ethics Committee (decision number: 21-5T/118, date: 20.05.2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: N.K., C.B., D.Y.K., Y.A., K.K., Concept: N.K., C.B., D.Y.K., Y.A., K.K., Design: N.K., C.B., D.Y.K., K.K., Data Collection and/or Processing: N.K., Analysis and/or Interpretation: N.K., C.B., D.Y.K., Y.A., K.K., Literature Search: N.K., C.B., D.Y.K., K.K., Writing: N.K., C.B., K.K.

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