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LETTER TO THE EDITOR

Diagnostic evaluation of the first macroscopic haematuria episode in adult haemophilia patients

Dear editor,

Recent retrospective studies in haemophilia patients reported prevalence of macroscopic haematuria ranging from 3.0% to 10.4%.[1,2] In three studies, 69% of haemophilia patients of all ages, 66% of adult haemophilia patients and 52% of haemophilia patients older than 40 years reported a lifetime event of macroscopic haematuria.[3–5] The World Federation for Haemophilia (WFH) recently updated their guidelines for the management of haemophilia.[6] In case of urinary tract haemorrhage, site of bleeding should be identified and treatment should immediately be administered. Only in case of recurrent or persistent macroscopic haematuria, patients should be referred to a urologist to assess a possible local aetiology. For the general (non-haemophilia) population various international guidelines are available for the evaluation of (macroscopic) haematuria, which generally advise urinalysis combined with a malignancy risk-based imaging strategy.[7,8]

Despite the WFH guideline, worldwide clinical practice in case of macroscopic haematuria in haemophilia differs.[6] Furthermore, reported outcomes of diagnostic evaluation in haemophilia patients with macroscopic haematuria are limited despite its high frequency. Therefore, we initiated the present study to evaluate outcomes of diagnostic evaluation of haemophilia patients at the first-lifetime episode of spontaneous macroscopic haematuria. Subsequent outcomes were also evaluated in light of current macroscopic haematuria guidelines for haemophilia patients and for the general population.

Adult haemophilia (A and B) patients treated at the haemophilia treatment centre of the Erasmus University Medical Centre, Rotterdam, the Netherlands, from January 2015 until December 2020 were screened for study inclusion. The study was not subject to the Medical Research Involving Human Subjects Act (WMO) and was approved by the Committee of Medical Ethics of the Erasmus University Medical Centre Rotterdam, the Netherlands, for data collection and analysis (MEC-2020-0683). Patients with at least one reported macroscopic haematuria episode in their medical history were included. Baseline characteristics, information on haematuria episodes and the results of diagnostic evaluation, such as urinalysis, imaging (CT, ultrasonography or plain radiography) and cystoscopy, were collected from available medical files of included patients. Haematuria aetiology was based on results of the diagnostic evaluation and clinical judgment. Kaplan-Meier analysis with log-rank test was performed to assess difference in age at the first-lifetime episode of macroscopic haematuria between severe and non-severe haemophilia with alpha <.05 for statistical significance.

In total 271 adult haemophilia A patients and 33 haemophilia B patients were assessed for inclusion. Forty-one (14%) patients had experienced at least one episode of macroscopic haematuria of whom six of iatrogenic aetiology; prostatectomy, mechanical manipulation of urinary catheter (two patients), prostate biopsy and urethra stricture dilation. In total, thirty-five patients had spontaneous haematuria and were included; 30 (86%) haemophilia A and 5 (14%) haemophilia B patients (Table 1). One haemophilia A patient also had mild type 1 von Willebrand disease. Eleven out of 35 (31%) patients had severe haemophilia, 8/35 (23%) moderate and 16/35 (46%) mild. In patients with severe haemophilia, eight out of eleven (73%) were on regular prophylactic treatment with clotting factor concentrate at the time of the haematuria episode. A single lifetime episode of macroscopic haematuria was reported in 16/35 (46%) patients. The remaining patients subsequently had persistent (4/35 (11%)) haematuria, defined as a new presentation of haematuria <3 months after the first episode, or recurrent (15/35 (43%)) haematuria, defined as a new presentation of haematuria ≥3 months after the first episode. Median age at first episode of macroscopic haematuria was 33 years (IQR 20–40), which did not differ between severe and non-severe haemophilia patients (24 years vs. 33 years; $p = .126$). However, all severe haemophilia patients had their first documented lifetime haematuria before 40 years of age.

In 31 of 35 (89%) patients diagnostic evaluation was performed at the first-lifetime episode of macroscopic haematuria and nineteen of these (61%) patients underwent more than one diagnostic test. The most used combination was urinalysis and ultrasonography (12/31; 39% patients). Evaluation per patient consisted of urinalysis (21/31; 68%), imaging (19/31; 61%), which was mainly ultrasonography (13/19; 68%), and cystoscopy (6/31; 19%). Diagnostic evaluation revealed an identifiable cause in 8/31 (26%) patients (Table 2). Imaging was pivotal in aetiology detection for six patients, of which four by ultrasonography. Cystoscopy revealed one diagnosis as did urinalysis. About half of the patients who underwent diagnostic evaluation (16/31; 52%) were referred to a urologist at time of the first haematuria episode. In these 16 patients, seven of the in total eight haematuria causes were found. In one patient, diagnosis was found without referral to a urologist (renal contusion on CT imaging).

Of all 35 patients, nineteen patients (54%) had either persistent haematuria (four patients) or at least one recurrent haematuria episode (fifteen patients). In four patients (4/19; 21%) haematuria aetiology was found with diagnostic evaluation performed at persistence

TABLE 1 Inclusion and patient characteristics ($n = 35$ after inclusion)

Characteristics	Number (%)/median [IQR]
Haemophilia treatment centre: cohort of haemophilia A patients	271 patients assessed, 30 patients included.
Severe	46 (17%)
Moderate	46 (17%)
Mild	179 (66%)
Haemophilia treatment centre: cohort of haemophilia B patients	33 patients assessed, 5 patients included.
Severe	9 (27%)
Moderate	8 (24%)
Mild	16 (49%)
Haematuria episode included patients ($n = 35$)	
Single lifetime	16 (46%)
Recurrent/persistent	19 (54%)
Severity haemophilia included patients ($n = 35$)	
Severe	11 (31%)
Moderate	8 (23%)
Mild	16 (46%)
Age at first episode of haematuria ($n = 33$[a]) included patients	
Severe haemophilia ($n = 10$), years	24 [20–37]
Moderate haemophilia ($n = 8$), years	35 [22–47]
Mild haemophilia ($n = 15$), years	33 [21–41]
Aetiology found with diagnostic evaluation at first-lifetime episode? ($n = 31$[b])	
Yes	8 (26%)
No	23 (74%)

[a]Two patients had missing data on age of first episode.
[b]Four patients had missing data on evaluation at first episode.

TABLE 2 Diagnostic evaluation of first macroscopic haematuria episode and at time of persistence of haematuria ($n = 35$)

First episode and patients with reported findings					
Evaluation	***Performed***	***Findings***	***Description (number)***	***Severity***	***Age***
Urinalysis (+ culture)	21	1	Pyelonephritis[a]	Mild[a]	44[a] years
Urine cytology	1	0	-	-	-
Ultrasonography	13	5	Urolithiasis (2)[a]	Mild[a], mild	44[a], 41 years
			Testicular torsion	Severe	17 years
			Prostatitis	Mild	23 years
			Medullary sponge kidney[b]	Mild	24 years
CT scan	3	2	Renal contusion	Severe	33 years
			Cortical kidney cyst[b]	Mild	45 years
Intravenous pyelogram	5	1	Urolithiasis	Moderate	37 years
Plain radiography	7	2	Urolithiasis (2)[c]	Mild[c], severe	85[c], 40 years
Cystoscopy	6	1	Urolithiasis/bladder lesion[c]	Mild[c]	85[c] years

[a]One patient had both urolithiasis and pyelonephritis simultaneously at time of evaluation.
[b]Of unknown significance as a haematuria aetiology, possibly related.
[c]One patient had urolithiasis at time of first episode, urothelial carcinoma at persistence (possibly related to bladder lesion).

or first recurrence. Of these four patients, one did not have a diagnostic evaluation at the first haematuria episode, one did have a diagnostic evaluation with no detected aetiology at the first episode and two with a detected aetiology at the first episode.

To summarize our results, spontaneous macroscopic haematuria was reported in 12% of our study cohort of adult patients with haemophilia, of whom 89% underwent diagnostic evaluation. In 26% of these patients, a cause could be detected. Of all diagnostic tools, imaging was the most effective in detecting haematuria aetiology, especially ultrasonography. Half of the evaluated patients was referred to a urologist.

In patients with haemophilia, macroscopic haematuria is considered to be benign and is usually attributed to the underlying bleeding disorder.[9] However, in our study in a quarter of the evaluated patients a cause for the haematuria was found, including malignancy in one patient. The current WFH guidelines state that older patients with haematuria have a higher risk for malignancy, but does not specify age or method for bleeding site identification in case of a urinary tract haemorrhage.[6] Considering the ubiquity of urinalysis and the effectiveness of imaging (ultrasonography) in our study we suggest to consider these tests in all haemophilia patients with a first macroscopic haematuria. This strategy is comparable to strategies used for macroscopic haematuria in the general population. In addition, this strategy could prevent persistent haematuria leading to extensive use of clotting factor concentrate with a risk for inhibitor formation. The WFH guidelines only advise referral to a urologist in case of persistence or recurrence.[6] In our study, the haematuria aetiology was detected in 44% of the patients referred to a urologist. This may be due to the fact that patients more likely to have a detectable haematuria cause (e.g., with pain, no resolution after a single administration of FVIII concentrate) were all referred. We, therefore, suggest that the initial diagnostic evaluation at the first episode should include referral to a urologist in case of a high risk for malignancy, such as age above 50 years and smoking, in accordance with guidelines for the general population. A supporting finding for this strategy is that in patients with macroscopic haematuria using anticoagulants—with also a higher bleeding risk—have an equal risk in finding a malignancy after diagnostic evaluation when compared to the general population.[10] Consequently, sequelae of late diagnosis of a malignancy can be prevented. In our study, only one patient was eventually diagnosed with a malignancy. This is probably related to the relatively young age of the included patients, as a urinary tract malignancy is usually diagnosed in patients older than 40 years. Additionally, the proposed strategy could prevent the extended use of clotting factor concentrate in case of treatable haematuria aetiologies, such as urinary tract infection. However, our study was not performed with a cost-effectiveness analysis in mind.

The most common cause of haematuria in our study was urolithiasis. A possible hypothesis for this is the increased urinary calcium excretion caused by repeated joint bleeds.[1] The use of older imaging modalities in our cohort such as plain radiography, could have led to an underreporting as non-radiopaque stones might have been missed. In addition, this could explain the early age of the first-lifetime haematuria episode in the severe haemophilia patients, as (spontaneous) joint bleeds are more common in severe than non-severe haemophilia.

Our study has certain limitations related to its retrospective character. Information bias could have been introduced as our cohort is based on retrospective data. However, we expect an underreporting of haematuria causes as not all patients in our cohort had received a diagnostic evaluation. Nonetheless, a majority of our patients still underwent further analysis.

In conclusion, spontaneous macroscopic haematuria in haemophilia patients can be the first sign of underlying pathology. In approximately a quarter of the evaluated patients, an underlying cause was found. Therefore, evaluation at first episode including urinalysis and ultrasonography is indicated to treat accordingly, comparable to guidelines for the general population. Referral to a urologist should be considered in case of a high risk for malignancy.

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LR designed the study, analyzed the data, performed research and wrote the manuscript. GM designed the study and critically revised the manuscript. MK designed the study and critically revised the manuscript. SC designed the study and critically revised the manuscript. IvM, MB, FL critically revised the manuscript.

DECLARATION OF INTEREST

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DATA SHARING STATEMENT

For original data, please send a reasonable request to m.kruip@erasmusmc.nl.

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