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Evaluation of Etiological Causes in Children with Symptomatic Hematuria

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Abstract

Hematuria is an important and common symptom of urinary system pathologies in children, and careful evaluation is required for its definitive diagnosis. This study aimed to determine the demographic and clinical characteristics and etiological causes of patients who applied to our pediatric nephrology clinic with hematuria. In this study, the record of 434 patients who were followed up in our clinic for macroscopic and/or microscopic hematuria were evaluated retrospectively. Demographic data, clinical findings, laboratory and imaging examinations, and final diagnosis of the patients were recorded. Out of 434 patients with hematuria, 239 (55%) were males and 195 (45%) females. Of the patients, 291 (67%) had macroscopic hematuria, and 83 (19.1%) had glomerular hematuria. Non-glomerular causes were found in 80.9%, with a significantly higher rate. Most of the causes of non-glomerular hematuria were urinary tract infection and renal stones. Acute post-streptococcal glomerulonephritis (APSGN) was found to be responsible for the majority of glomerular diseases. This study shows that most pathologies that may cause hematuria can be detected with a detailed history, careful physical examination, and simple laboratory tests.

Keywords: Hematuria, children, etiology, glomerular, non-glomerular

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Introduction

Hematuria is one of the important symptoms encountered in the pediatric age group. It may occur as an initial sign of urinary system disease. It can be macroscopic or microscopic and symptomatic or asymptomatic. The presence of hematuria is indicative of a wide variety of etiologies. Hematuria is defined as centrifuged urine residue containing more than five red blood cells (RBCs) in a 40x magnification field under light microscopy.[1] The prevalence of microscopic hematuria varies between 0.15-2%. with an estimated incidence of 1.3 per 1000 children.[2,3]

Hematuria can originate from the upper or lower urinary tract. The upper urinary tract sources are the glomerulus, tubular system, or interstitium. The pelvicalyceal system, ureter, bladder, and urethra are sources of hematuria in the lower urinary tract.[4,5] The diagnosis of hematuria is made with a detailed history, systemic physical examination, and laboratory tests. In urine microscopy, the presence of dysmorphic RBC with distorted contours is typical for almost glomerular hematuria.[6]

Highlights

- Hematuria is one of the important symptoms in the pediatric age group.
- It can be macroscopic or microscopic and symptomatic or asymptomatic.
- The presence of irregular, dysmorphic RBC with distorted contours in urine microscopy indicates the outflow of erythrocytes from the glomerular capillaries into the urinary cavity and is almost pathognomonic for glomerular hematuria.

Under physiological conditions, endothelin windows (50-100 nm) are thought to act as self-contained molecular-sized sieves to keep RBCs (6.2-8.2 µm) away from the glomerular basement membrane (GBM). How RBCs that are 100 times larger than the pores of the glomerular endothelium cross the GBM remains unclear. The release of inflammatory or chemotactic signals that promote RBC passage through a damaged glomerular filtration barrier (GFB) layer has been implicated, but specific mechanisms have yet to be clarified.[7] The change in the morphology of erythrocytes is due to mechanical damage as they pass through the glomerular basement membrane and osmotic damage as they pass through the nephron. Therefore, glomerular hematuria indicates dysfunction and damage to the glomerular basement membrane.[8]

Knowing the causes of hematuria and their frequency facilitates the approach of clinicians. This study aimed to determine the demographic, clinical characteristics, and etiological causes of patients who applied to our pediatric nephrology clinic between 2016 and 2021 with symptomatic hematuria.

Material and Method

The records of 434 patients who were followed up in Fırat University Pediatric Nephrology Clinic between 01 July 2016 and 30 June 2021 due to macroscopic and/or microscopic hematuria were evaluated retrospectively. Patients with red urine but no erythrocyte detected in urine microscopy were not included. Demographic data, onset and duration of signs and symptoms, clinical findings, family history of chronic kidney disease, and laboratory results were recorded. The study was approved by the ethics committee of Fırat University on the 10.02.2022 date and with an issue protocol number of 2022-02-17. Macroscopic hematuria may be bright red or brown-colored with or without visible clots. Microscopic hematuria is defined as a significant number of red blood cells (>5/HPF) in the urine without color change. After the urine of the patients was centrifuged at 2000 rpm (revolutions per minute) for 10 minutes for microscopic examination, the presence of five or more erythrocytes at 40x magnification was defined as hematuria.[1] Glomerular hematuria was differentiated from non-glomerular hematuria by the presence of dysmorphic RBCs, erythrocyte cast, and proteinuria.[9]

In addition, urinalysis, complete blood count, coagulation parameters, urea, creatinine, total protein, albumin, serum electrolytes, and urinary ultrasonography information was recorded. Anti-streptolysin O titers, throat culture, urine culture, antinuclear antibodies, anti dsDNA antibodies, peripheral and cytoplasmic nuclear antibodies were measured in selected patients for diagnosis. The patients who underwent computed tomography and magnetic resonance imaging within the indications were scanned. Ophthalmologic and audiometric examinations were reviewed in patients with a family history of chronic kidney disease, Alport's disease, hematuria, deafness, and/or ophthalmologic problems. Renal biopsy was performed in selected cases such as unidentified and recurrent macroscopic hematuria, microscopic hematuria with proteinuria lasting longer than six months, family history of hematuria, or end-stage renal disease suggestive of glomerular disease.[1] The patients' data were recorded, and their final diagnoses were evaluated.

Statistical analysis was performed with the IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp.). Data were expressed as the median and interquartile range for quantitative nonparametric measures as the mean and standard deviation (SD) for parametric data.

Results

Out of 434 patients with macroscopic or microscopic hematuria, 239 (55%) were male, and 195 (45%) were female, with a male/female ratio of 1.22 (**Table 1**). The mean age of the patients was seven years and six months (between 1 month and 17 years). At admission, red urine was the first complaint, with a rate of 46%. Followed by abdominal pain with 12.4%, dysuria with 6.2%, and fever with 5.2%. While the complaint of swelling in the body was 5.2%, the rash rate was 3.2%. Other complaints (21%) included decreased urine, inability to urinate, decreased feeding, restlessness, vomiting, sore throat, cough, constipation, joint pain, diarrhea, urinary incontinence, and nose bleeding. While 292 (67%) patients had macroscopic hematuria, 143 (33%) patients had microscopic hematuria. In light microscopy, 80.9% of the erythrocytes were morphic, and non-glomerular hematuria was detected. In

comparison, 19.1% of them were found to have glomerular hematuria with the presence of dysmorphic erythrocytes and erythrocyte casts (**Table 2**).

Table 1
Distribution of hematuria cases according to age groups and gender

Age	Female n	Male n	Total n	%
0-5	68	83	151	34.7
6-11	80	97	177	40.8
12-18	47	59	106	24.5
Total	195	239	434	100

Table 2
Classification of patients with symptomatic hematuria

Etiology	n (434)	%
Glomerular diseases	83	19.1
Non-glomerular diseases	351	80.9

Out of 83 (19.1%) patients with glomerular hematuria, 36.3% were acute post-streptococcal glomerulonephritis, the first among glomerular causes. This was followed by nephrotic syndrome with 24% and Henoch Schönlein Purpura (HSP) nephritis with 16.8%. Other causes of glomerular hematuria were Alport's disease, IgA nephropathy, thin basement membrane disease, and Wegener's granulomatosis (**Table 3**).

Table 3
Diagnosis of patients with glomerular hematuria

Glomerular diseases	n (83)	%
APSGN	30	36.3
Nephrotic syndrome	20	24.1
HSP	14	16.8
Alport's Disease	4	4.8
Ig A nephropathy	3	3.6
FMF	6	7.2
HUS	5	6.0
Wegener's granulomatosis	1	0.2

APSGN: Acute poststreptococcal glomerulonephritis, HSP: Henoch Schonlein Purpura, FMF: familial mediterranean fever, HUS: hemolytic uremic syndrome

Urinary tract infection was the most common cause in 42% of 351 patients with non-glomerular hematuria. This was followed by nephrolithiasis, upper respiratory tract infection, crystalluria, obstructive uropathy, nutcracker syndrome, and idiopathic causes. More rarely, other causes such as thrombocytopenia, menstruation, dehydration, trauma, exercise, hemolytic anemia, sexual abuse, left accessory renal vein, celiac disease, and renal cyst were recorded (**Table 4**).

Table 4
Diagnosis of patients with non-glomerular hematuria

Non-glomerular Diseases	n (351)	%
Urinary tract infection	149	42
Renal stone	60	17
Upper respiratory tract infection	27	7.6
Crystalluria	12	3.5
Obstructive uropathy	10	2.8
Nutcracker Syndrome	8	2.2
Other causes	31	9.1
Idiopathic causes	54	15.8

Other causes: Heavy exercise, trauma, thrombocytopenia, hemolytic anemia menstruation, sexual abuse, renal cyst, nephrocalcinosis, dehydration, celiac disease.

Computed tomography was performed in 31 (7.4%) patients; magnetic resonance imaging was performed in 6 (1.3%) patients. Among the patients with glomerular hematuria, 29 patients (6.6% of all patients) underwent kidney biopsy within the indications. Considering the distribution of patients who underwent kidney biopsy by years, there was no significant difference, and approximately 50% were performed within the last two years. Of 29 patients who underwent kidney biopsy, 9 had membranoproliferative glomerulonephritis (MPGN), 7 had HSP nephritis, 6 had APSGN, 3 had IgA nephropathy, 2 had focal segmental glomerulosclerosis (FSGS), one had Alport's disease, and one had thin membrane disease.

Discussion

Hematuria is a worrying condition for both the family and the child. It can be asymptomatic and a symptom of severe kidney disease. Macroscopic hematuria is a significant health problem that causes families to seek immediate medical attention. Microscopic hematuria is often detected incidentally or during school or community screening programs and is more common than macroscopic hematuria.[10-12] As our study included patients presenting with symptoms, macroscopic hematuria was found more frequently than microscopic hematuria (67% versus 33%). Another study was conducted by Youn T. et al.[13] was performed on the medical records of 1001 children and adolescent patients with gross hematuria. Glomerular gross hematuria was found in 24 patients, and the cause was most commonly Ig A nephropathy. Alport's syndrome non-glomerular gross hematuria was found in 56 patients, and the most common etiologies were hypercalciuria, urethrorrhagia, and hemorrhagic cystitis. No etiology was found in 26 patients. Arı et al.[14] conducted a retrospective study with 370 pediatric patients, whose mean age was 7 ± 3.5 years, 52% boys and 48% girls and similar to our research, they found a higher rate of macroscopic hematuria than microscopic hematuria; also non-glomerular causes were detected more frequently with a rate of 72.4%. In our study, non-glomerular causes were seen at a rate of 80.9%, and they were more common than glomerular causes. By the literature, the most common non-glomerular cause was urinary tract infection, followed by renal stone.

It is known that a systematic approach is required after a detailed history and careful physical examination to determine the cause in a pediatric patient with hematuria. Symptoms determined by a thorough history will be helpful for the clinician to reach the diagnosis from signs and prevent unnecessary laboratory tests. It would be appropriate to perform step-by-step tests to confirm the diagnosis according to the findings detected in the patient after the initial evaluation. (**Figure 1**). Renal Doppler ultrasonography is a recommended method for imaging, especially in cases of unexplained hematuria with or without abdominal pain. According to reports, Nutcracker syndrome is one of the leading causes in children with isolated hematuria and proteinuria without urinary tract infection. Renal Doppler ultrasonography is considered the first screening tool to detect nutcracker syndrome.[15,16] Shin et al.[16] detected nutcracker syndrome in 60 of 149 patients with isolated hematuria. In another study evaluating the

etiology of hematuria in children, it was reported that NS was seen in 0.7% of the cases.[14] In our study, nutcracker syndrome was found in 2.2% of patients with hematuria.

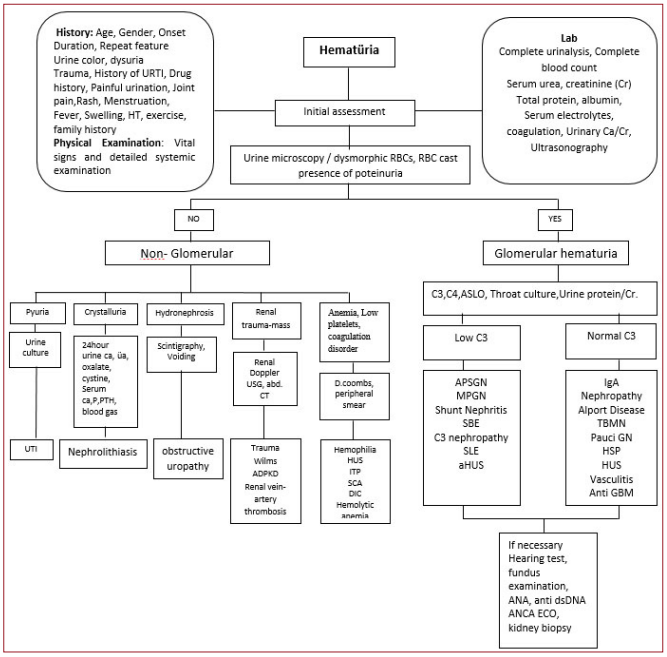

Figure 1. Diagnostic algorithm for hermaturia

URTI: Upper respiratory tract infection, UTI: Urinary tract infection Ca: calcium, P: phosphate, APSGN: Acute poststreptococcal glomerulonephritis, HSP: Henoch Schonlein Purpura, , HUS: Hemolytic uremic syndrome , SBE: Subacute bacterial endocarditis, TBMN: Thin glomerular basement membrane disease, SCA: sickle cell anemia C3: complement factor 3, ASLO: antistreptolysin O, CBC: complete blood, C4: Complement factor 4, ANA: Antinuclear antibody, anti dsDNA: Anti-doublestranded DNA antibody, ANCA: Antineutrophil cytoplasmic, ECO: Echocardiography

A 10-year retrospective review of 342 children who presented with gross hematuria to a pediatric urologic center in the United States reported that no cause could be determined in 35% of the patients.[17] However, in our study, 15% of the patients had no cause that could be determined.

Kidney biopsy is indicated in selected patients with hematuria. The presence of a family history of hematuria or nephritis, accompanying proteinuria, prolonged hypocomplementemia and hypertension, persistent microscopic hematuria, or recurrent macroscopic hematuria are common indications for renal biopsy.[18,19] In this study, 29 (6.6%) of the patients underwent renal biopsy, and the most common histopathological finding was MPGN. Although IgA nephropathy was the most common finding in Lee et al.[20] we think that the rarity of IgA nephropathy in our study is that it only included cases with symptoms.

Conclusion

In this study, we found that the etiology of the majority of patients who applied to our tertiary clinic in the eastern region of our country (Turkey) with hematuria could be clarified as a result of detailed history, detailed physical examination, and basic laboratory tests that could be performed in a secondary health institution. Further imaging studies and renal biopsy are indicated in selected cases.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Fırat University Ethics Committee (Date: 10.02.2022, Decision No: 2022-02-17).

Financial Disclosure: The authors have no conflicts of interest to declare.

Informed Consent: Informed consent was obtained from the parents of the patients.

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