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CLINICAL AND BIOLOGICAL ASPECTS OF HEMATURIA IN CHILDREN

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Abstract

Introduction: Hematuria is very common in childhood but if it persists in multiple urine examinations it deserves further detailed evaluation. Hematuria is the increased excretion of erythrocytes in the urine. It can be macroscopic or microscopic. It is a finding of more than 5 erythrocytes/hpf in the urine sediment.

This study aims to analyze demographic and etiological characteristics of hematuria in children, to determine the diagnostic value of urine calcium, proteinuria, and ultrasound findings in both forms of hematuria, microscopic and macroscopic.

Material and methods: The study includes 150 children aged 1-16 years, with confirmed hematuria in the January 2020 - February 2022 period at the University Children's Hospital - Skopje. Patients are divided into two groups: the group with macroscopic and the group with microscopic hematuria. The two groups are compared in terms of ultrasound findings, urine calcium, and proteinuria. Familial urinary screening for hematuria was also performed.

Results: Of 150 children, 59.33% had microscopic and 40.67% macroscopic hematuria.

The most common proven etiology in microscopic hematuria is familial hematuria (34.83%), while in macroscopic hematuria the most common cause is glomerulonephritis (39.34%). Hypercalciuria was found in 5 (6%) of the examined children. Proteinuria is significantly higher in the gross hematuria group. Of the 80 screened families, 35 were found to have a familial form of hematuria.

Conclusion: This study indicates the frequency of familial hematuria and the importance of familial screening. The values of urine calcium and ultrasound finding do not have a statistically significant difference between the two groups, while proteinuria is higher in macroscopic hematuria ($p < 0.05$).

Keywords: hematuria, macroscopic, microscopic, children.

Introduction

Hematuria is a common problem in pediatric practice. Many pediatricians routinely screen urine for hematuria and proteinuria. As an incidental finding, hematuria is very common in childhood; however, if it persists in multiple urine examinations, it deserves further detailed evaluation.

Hematuria represents increased excretion of erythrocytes in urine.

It can be macroscopic - visible with the naked eye or microscopic. The standard method for proving hematuria is a microscopic examination of a fresh urine sample. Confirmation of hematuria is based on a finding of ≥ 5 erythrocytes/high-power field in the sediment of a centrifuged urine.

Microscopic examination of urine sediment also reveals the presence of erythrocyte cylinders, and dysmorphic erythrocytes suggesting glomerular hematuria. In ambulatory practice, a quick and helpful method for examining urine is testing with dipsticks impregnated with ortho-Toluidine. The test is also positive for free hemoglobin and myoglobin, so any positive finding should be confirmed with subsequent microscopic examination [1-4].

Hematuria can also be associated with proteinuria. According to the origin of erythrocytes in urine, hematuria is divided into glomerular and non-glomerular hematuria [5-8].

Microscopic hematuria is present in 1% of children, while in 30% of them persists for more than 6 months. The incidence of macroscopic hematuria in children is 0.13% [9-12].

The etiology of hematuria is very heterogeneous, the most common etiology in glomerular hematuria is: post-infectious glomerulonephritis, IgA nephropathy, thin basement membrane disease, Alport syndrome, Henoch Schönlein purpura, hemolytic uremic syndrome, membranoproliferative glomerulonephritis, lupus nephritis, etc., while the most common causes in non-glomerular hematuria are urinary tract infections, congenital anomalies of the urinary tract, trauma, hypercalciuria, urolithiasis, tumors, coagulopathy, intensive physical exertion, etc [13, 14].

Clinical evaluation of children with any form of hematuria begins with a detailed history. Physical status includes measurement of body height and weight, blood pressure, detailed physical examination for the presence of fever, edema, skin rash, abdominal mass, nephromegaly, costovertebral angle tenderness, examination of the genital and anal region, determination of hearing, etc. When examining urine for hematuria, it is necessary to perform a metabolic profile, to determine calciuria, uricosuria, oxaluria, citraturia, and magnesiuria [15, 16].

Further diagnostic processing is aimed at determining renal function, complement system factors, antistreptolysin O titer, electrolytes, serum proteins, and lipids. Imaging studies are also needed, usually an ultrasound examination of the urinary tract and sometimes a computerized tomography or magnetic resonance [17].

An important diagnostic method in the evaluation of hematuria is a kidney biopsy. In certain conditions, such as glomerulonephritis of unclear etiology, azotemia, and hypertension, it is absolutely indicated. However, the indication for renal biopsy in isolated hematuria is still arguable, in a such situation very few centers perform a biopsy. Of the published studies with biopsies performed in isolated microhematuria, a large percentage of them have glomerular abnormalities, thin basement membrane disease, IgA nephropathy, and Alport syndrome [18, 19].

Molecular genetic analysis for the presence of a mutation in COL4A3-A5 genes has recently replaced kidney biopsy in familial hematuria. In fact, 30-50% of children with isolated glomerular hematuria belong to the two major forms of familial hematuria, Alport syndrome, and thin basement membrane disease.

A detailed family history allows the identification of relatives with hematuria, renal failure, or deafness and is therefore an important step in the evaluation of children with hematuria. The next and very important step is family screening for hematuria of all members of the child's close family (parents, siblings). Early genetic diagnosis enables genetic counseling in the family, close monitoring of the patient, and early treatment with inhibitors of the renin-angiotensin-aldosterone system, thereby delaying the development of end-stage renal failure [20-24].

Objectives

To analyze the demographic and etiological characteristics of children with hematuria. To determine the diagnostic value of calciuria, proteinuria, and ultrasound findings in both forms of hematuria, microscopic and macroscopic.

Material and methods

The study includes 150 children with confirmed hematuria in the January 2020 - February 2022 period, at the University Children’s Hospital – Skopje. Data were taken from a patient's history and an outpatient examination report. Hematuria is defined as the finding of 5 or more erythrocytes/hpf in urine sediment in two consecutive urine samples. Patients are divided into two groups: a group with macroscopic and a group with microscopic hematuria.

Workup of patients includes a detailed family history of kidney disease in the family, urolithiasis, and other hereditary diseases. This is then followed by a detailed physical examination, with measurement of body weight and arterial blood pressure, and an ultrasound examination of the urinary tract. Laboratory studies include biochemical studies to define the etiology of hematuria. Family screening for hematuria was performed in a certain number of patients, especially those with persistent hematuria.

Calciuria is determined in a urine sample or in a 24-hour urine collection. Cut-off values of calciuria are calcium/creatinine ratio for children under 1 year >2.2 mmol/mmol, 1-2 years >1.5 mmol/mmol, 2-3

years >1.4 mmol/mmol, 3-5 years >1.1 mmol/mmol, 5-7 years >0.8 mmol/mmol, and for children over 7 years >0.7 mmol/mmol or value >4 mg/kg body weight in a 24-hour urine collection. Quantifying proteinuria is determined in two ways: 1) in a urine sample as a protein/creatinine ratio (mg/mmol) where a normal finding is considered <20, mild to moderate proteinuria 20-200, while a nephrotic range of proteinuria is considered ratio > 200 or 2) in a 24-hour urine collection where values up to 150 mg/24 hours are taken as normal values, nephrotic range of proteinuria is defined as > 50 mg/kg/day.

Ultrasound examination of the urinary tract was categorized into two categories: normal ultrasound findings and abnormal ultrasound findings. Any deviation from the normal size, morphology, and structure of the urinary tract is considered abnormal as congenital anomalies of kidneys and urinary tract, hydronephrosis/hydroureter, duplex collecting system, agenesis, hypoplasia/dysplasia, ectopic kidney, arcuate kidney, impaired echogenicity of renal parenchyma, presence of cysts in kidneys, calculus, tumor formation, nephrocalcinosis, nephrectomy, thickened bladder wall, ureterocele, etc. Both groups were compared in terms of ultrasound findings, calciuria, and proteinuria.

Statistical analysis was conducted with SPSS software for Windows version 26. Categorical variables between the two groups were compared with the Chi-square test ($\chi 2$), while low frequencies were with the Fisher exact test. The value of $p<0.05$ was taken as a statistically significant difference.

Results

The study includes 150 patients with hematuria aged 1 to 16 years who were treated at the University Children's Hospital - Skopje, in January 2020 to February 2022 period, of which 79 children are male and 71 are female. The demographic characteristics of the children are shown in Table no. 1.

Table 1. Demographic characteristics of children with hematuria.

	Number (N)	**%**
Total patients	150	100%
Gender		
Male	79	52.7%
Female	71	47.3%
Age		
0-5 y	53	35.3%
6-10 y	65	43.3%
11-16 y	32	21.3%
Ethnicity		
Macedonian	75	50%
Albanian	52	34.7%
Roma	20	13.3%
Other	3	2%

In most children, microscopic hematuria is present in 89 children, 59.3% of the total number, while macroscopic hematuria is present in 61 children or 40.7%. There is no significant difference regarding the gender and age of the children in terms of the type of hematuria - macroscopic and microscopic hematuria (Tables no. 2 and 3).

Table 2. Patients by gender and type of hematuria

	Number (%) of children by type of hematuria			
Gender	Macrohematuria	Microhematuria	Total	*P
Male	37	42	79	1.342
Female	24	47	71	
Total	61	89	150	

*Chi-square test ($\chi 2$ test), $p<0.05$

Table 3. Patients according to age groups and type of hematuria

	Number (%) of children by type of hematuria			
Age	Macrohematuria	Microhematuria	Total	*P
0-5 y	16	37	53	.144
6-10 y	31	34	65	
11-16 y	14	18	32	
Total	61	89	150	

*Chi-square test ($\chi 2$ test), $p<0.05$

According to etiology, patients are placed into several groups. In the group of urinary infections, 10/27 had a congenital anomaly of the urinary tract and also had a urinary infection at the time of hematuria. In the group of congenital anomalies of the urinary tract, patients with hydronephrosis but without signs of infection were placed. In the glomerulonephritis group, 22 had acute post-streptococcal glomerulonephritis, 4 were IgA nephropathy, and 2 were undifferentiated.

The group of familial hematuria includes children with persistent hematuria who have one or more family members with hematuria, while that group includes 35 children. There are 31 children with undefined hematuria, 18 with macrohematuria, and 13 with microhematuria in whom until now it was not possible to determine the cause of hematuria. In the group of children with urolithiasis, two children have a rare genetic disease, one with primary hyperoxaluria type 1 and one with cystinuria. Microscopic hematuria is more common in urinary infections (p=.002) and familial hematuria (p=.000), while macroscopic hematuria is more common in glomerulonephritis (p=.000) and undefined hematuria (p=.039) (Table no. 4).

Table 4. Etiology of macroscopic and microscopic hematuria.

	Macrohematuria		**Microhematuria**			
	Number	%	Number	%	Total	
From the total number of patients (N=150)	61	40.67%	89	59.33%		
Etiology						*P
Urinary infections	4	6.56%	23	25.85%	27	**0.002**
Congenital anomalies	1	1.64%	4	4.49%	5	0.648
Glomerulonephritis	24	39.34%	4	4.49%	28	**0.000**
Urolithiasis	4	6.56%	6	6.74%	10	1.00
Familial hematuria	4	6.56%	31	34.83%	35	**0.000**
Undefined hematuria	18	29.51%	13	14.61%	31	**0.039**
Nephrotic syndrome	/	/	3	3.37%	3	0.271
Hemolytic uremic syndrome	3	4.92%	/	/	3	0.063
Henoch Schonlein purpura	1	1.64%	1	1.13%	2	1.00
Other	2	3.27%	4	4.49%	6	

*****Fisher exact test, $p<0.05$

Both groups of children were compared in terms of ultrasound findings, calciuria, and proteinuria. An ultrasound examination was performed in 122 children, an abnormal finding was present in 41 children (33.6%). Hypercalciuria was present in 5/84 children, i.e., in 6%. Proteinuria of a moderate degree was present in 58/140 children, i.e., 41.4%, while proteinuria of the nephrotic range was present in 24/140 children, i.e., 17.2% of the children. A significant statistical difference between the two groups is present only concerning proteinuria (p=.01), i.e., in macrohematuria, the proteinuria is higher, while for calciuria and ultrasound findings there is no significant statistical difference between the two groups. (Table no. 5)

Table 5. Ultrasound finding, calciuria and proteinuria in macroscopic and microscopic hematuria.

		Microhematuria	**Macrohematuria**	**Total**	***P**
Ultrasound	Normal	46	35	81	0.335
	Abnormal	27	14	41	
				122	
Calciuria	Normal	39	40	79	0.645
	Hypercalciuria	3	2	5	
				84	
Proteinuria	Normal	42	16	58	**0.01**
	Moderate	26	32	58	
	Nephrotic range	13	11	24	
				140	

*Chi-square test ($\chi 2$ test), $p<0.05$

In children whose hematuria is persistent and the etiology cannot be clearly defined, screening of the family for hematuria was carried out. Out of 80 family screenings, a familial form of hematuria was confirmed in 35, that is, in 43.75%.

Discussion

Out of 150 children, in our study 79 (52.7%) were male while 71 (47.3%) were female, which does not correspond to published studies where the representation of the female gender is higher. Among the age groups, the group of 6-10 years is the most represented. [25-27].

However, statistically, the two groups compared in terms of gender and age have no significant difference. The large percentage of children of Roma nationality (13.3%) is due to a large representation of acute post-streptococcal glomerulonephritis among the Roma population due to the low socioeconomic status, of 22 children with acute post-streptococcal glomerulonephritis, 11 children are of Roma nationality (50%).

From our study group of 150 patients, macroscopic hematuria was present in 40.67% of children, while microscopic hematuria was present in 59.33%. The most common etiology in the group of macroscopic hematuria is glomerulonephritis (39.34%), while in the case of microscopic hematuria the most common is familial hematuria (34.83%) and urinary infections (25.85%). In our country, acute post-streptococcal glomerulonephritis is still a common occurrence, therefore the frequency of occurrence corresponds to studies published by developing countries [28].

In a relatively large percentage of children with macroscopic hematuria, the etiology remains undefined (29.51%), most often it is hematuria, which occurs once and does not repeat itself and all the investigations conducted are normal. In the study by Ingelfinger et al, 158 children with macroscopic hematuria were included, in 44% the cause was not evident, while in 26% a urinary tract infection was confirmed [12].

In our analysis and comparison between the two groups, calciuria, proteinuria, and ultrasound findings were considered as three very important methods for differentiating the etiology of hematuria. A

significant statistical difference is present only for proteinuria, which is expected because, in our group of macroscopic hematuria, a large percentage is a glomerulonephritis associated with significant proteinuria. Hypercalciuria has been reported in various studies to be present in 10-30% of patients with isolated microhematuria. In our series of patients, hypercalciuria was present in 5/84 or 6% of children [29-31].

In the group of patients with microscopic hematuria, the high percentage of children with familial hematuria (34.83%) is the most surprising. It is due to the mass urinary family screening that was carried out, in 80 out of 150 families. A positive finding (presence of one or more family members with hematuria) was obtained in 35 families. T

his indicates how important urinary screening of families is. Further genetic testing is necessary for confirming the diagnosis of Alport syndrome. According to the latest recommendations for the monitoring and treatment of Alport syndrome, therapy with renin-angiotensin-aldosterone system blockers is started immediately upon diagnosis in male children with X-linked form of Alport syndrome and autosomal recessive forms of the disease, while in female children heterozygotes for the mutation of the COL4A5 gene and in heterozygotes for mutation of the COL4A3 and COL4A4 genes, therapy is started at the stage of proteinuria above the permitted reference values [32-34].

Conclusion

The study showed the frequent occurrence of familial hematuria and the importance of familial screening. Calciuria values and ultrasound findings have no significant statistical difference between the two groups of macroscopic and microscopic hematuria, while proteinuria is higher in macroscopic hematuria ($p<0.05$).

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