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Prevalence of Microalbuminuria in Children with Asymptomatic Microscopic Hematuria

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Mastaneh Moghtaderi,*
Ali Yamini,
Marjan Vakili,
Tahere Khan mohmadi,
Azam Rahmani

Pediatric Nephrology Department, Children's Medical Center Hospital, Pediatric Center of Excellence, TUMS, Tehran, Iran.

*** Corresponding Author**
Mastaneh Moghtaderi, MD
Children's Medical Center Hospital, Tehran, Iran.
E-mail:
drmoghtaderi@gmail.com

Introduction: A wide range of chronic and acute diseases begin with asymptomatic microscopic hematuria. Simultaneous presence of microalbuminuria and microscopic hematuria is suggestive of an important kidney disease. The purpose of this study was to determine the prevalence of microalbuminuria in children with asymptomatic microscopic hematuria.
Materials and Methods: This cross-sectional study was done on 150 children aged 2-14 years with asymptomatic microscopic hematuria at Nephrology Clinic of Children's Hospital Medical Center in 2013-2015. All patients had clinical and laboratory tests such as BUN, creatinine, electrolytes, urine albumin/ creatinine ratio, blood pressure, etc. The obtained data were recorded and analyzed with SPSS (ver. 18). All children with anatomical anomalies, hypertension, previous urinary tract surgery, or nephrolithiasis were excluded from the study.
Results: The overall prevalence of microalbuminuria was 14.5 % and there was a significant relationship between microalbuminuria and the presence of dysmorphic red blood cells on urine analysis (p-value<0.05). The incidence of RBC cast was 54% (82 patients). Two children had upper-normal levels of blood pressure for age and sex that were followed closely and received special diets and medications. Twenty-nine patients (18.6%) had a positive family history of asymptomatic microscopic hematuria and the father of one of them had IgA nephropathy with ESRD. In children with microalbuminuria that received drugs for 3-28 months (mean, 6.3 months), microalbuminuria decreased significantly.
Conclusions: Isolated asymptomatic microscopic hematuria is a benign disease but its association with proteinuria may indicate a serious problem with the risk of progressive renal disease. It is recommended to determine the microalbumin/creatinine ratio in cases with asymptomatic microscopic hematuria.

Keywords: Asymptomatic Microscopic Hematuria; Microalbuminuria; Prevalence; Child.
Running Title: Prevalence of Microalbuminuria in Hematuria.

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Introduction

Microscopic hematuria is a common finding in healthy children. The prevalence of asymptomatic microscopic hematuria ranges from 0.19 - 21%. This wide range is largely due to differences in the age and sex of the study populations. The overall prevalence of isolated microscopic hematuria in children and adolescents is 1.5% [1]. General population screening studies have shown that the prevalence of hematuria, both macroscopic and microscopic, may range from 5% to 20% [2].

In one study, macroscopic hematuria had an estimated incidence of 1.3 in 1000 population. The incidence of microscopic hematuria in school children was estimated at 0.41% when four urine samples per child were collected and 0.32% in girls and 0.14% in boys when five consecutive urine specimens were analyzed over 5 years. In the majority of children, follow-up urinalyses became normal in the following years [3].

Urine dipsticks are commonly used to detect microscopic hematuria in laboratories. When used correctly, urine dipsticks have a sensitivity of 100% and a specificity of 99% to detect 1-5 RBCs/HPF, which is translated as 5-10 RBCs/μL of the urine. False-positive results can be seen in the presence of hemoglobin, myoglobin, or hypochlorite in the urine and false-negative results can be seen when the urine specific gravity is high or there are reducing agents like ascorbic acid in the urine [4].

There is a wide variety of diseases with microscopic hematuria, which are mostly benign, especially in children. Hematuria may originate from upper structures like glomeruli, renal tubules, and interstitium, or from the lower urinary tract (including the collecting system, ureter, bladder, or urethra) [5]. Unlike adults, the source of the bleeding in children is more often from the glomerular area rather than the lower urinary tract and can sometimes progress to renal failure if untreated [6].

In most people, hematuria originates from the lower urinary tract. Less than 10% of hematuria has a glomerular origin [7]. Depending on the source of bleeding, hematuria can be classified as glomerular with dysmorphic red cells and non-glomerular with isomorphic red cells in the urine. In case of non-glomerular hematuria, any factor that disrupts the uroepithelium such as irritation, inflammation, or invasion can result in normal appearing RBCs in the urine. Direct injury to the tubulointerstitium by infections, stones, and ischemic necrosis of the papillae can produce non-glomerular hematuria [8,9]. Glomerular diseases generally present with variable degrees of hematuria, RBC casts, proteinuria, and/or impaired renal function and hypertension, singly or in combination. Renal biopsy is the gold standard method for diagnosing GN, but it is an invasive and expensive procedure [10]. Concomitant presence of red cell casts and proteinuria also indicates a glomerular origin, but lower urinary tract problems, particularly tumors, hydronephrosis, or stones, must always be ruled out by careful studies like ultrasound examination. The renal papillae (as a source of hematuria) are susceptible to necrotic injury from microthrombi and anoxia in patients with a hemoglobinopathies or in those exposed to chemical toxins or drugs. Patients with renal parenchymal lesions may also have episodes of transient microscopic or macroscopic hematuria during systemic infections or after moderate exercise [11].

Materials and Methods

This cross-sectional study was done on 150 children with asymptomatic microscopic hematuria aged 2-14 years at Nephrology Clinic of Children's Medical Center in 2013-2015.

The patients were evaluated for blood pressure, renal function testes, dysmorphic RBCs, and RBC and casts in the urine. Urine culture was also requested for all patients. For some patients with dysmorphic RBC and casts on urinalysis, serum complement levels, ANA, hepatitis markers, and other laboratory tests were done to find any secondary upper urinary tract cause of microscopic hematuria. All children had screening urinary tract ultrasonography to find anomalies and microlithiasis.

Microalbuminuria in a random urine test is defined as a microalbumin /creatinine ratio more than 30 in at least two morning spot urine tests. In patients with microalbuminuria, we considered close fallow-up and prescribed drug such as ACE inhibitors. All children with anatomical anomalies, hypertension, previous urinary tract surgery, and nephrolithiasis were excluded from this study.

Results

There were 150 children with persistent asymptomatic microscopic hematuria. The sex distribution of the cases is shown in Table 1.

Table 1. Sex distribution of patients

Sex	Prevalence	%
Male	57	37%
Female	93	62%
Sum	150	100%

The prevalence of micro albuminuria in children with microscopic hematuria was 14% (21 patients). These patients received ACE inhibitors such as enalapril or ARBs such as losartan. The mean level of microalbuminuria before and after treatment is presented in Table 2. Two children had upper-normal levels of blood pressure that became normal after close fallow-up and receiving appropriate diets and drugs. Twenty-nine patients (18.6%) had a positive family history of asymptomatic microscopic hematuria and the father of one of them had IgA nephropathy with ESRD. As for laboratory findings, all children had normal electrolytes and renal function tests.

Table 2. Mean and SD of microalbuminuria, Bun, and Creatinine

Factor	mean	SD
Age(y)	6.68	3.18
BUN(mg/dl)	12.25	4.04
Cr(mg/dl)	0.57	0.22
MicAlb/Cr in children with microalbuminuria	68.50	27.06
MicAlb/Cr In children with non microalbuminuria	16.44	4.22
MicAlb/Cr In children with microalbuminuria after treatment	31.60	24.04

Ninety-two (54.6%) children had dysmorphic RBCs above 70% in at least 2 random spot urine tests, which was significant (P Value>0.1). The incidence of RBC casts was 14% (21 patients). In children with microalbuminuria that received drugs for 3-28 months (mean, 6.3 months), microalbuminuria decreased significantly. All children were followed for at least 3 years, and none of them developed decreased renal function, proteinuria, or hypertension.

Table 3. Relationship of microalbuminuria and dysmorphic RBC

Micro albuminuria	dysmorphic RBC		sum	P Value
	–	+		
Negative	61	68	129	0.019
Positive	7	14	21	
Sum	68	82	150	

Table 4. Efficacy of medical therapy before and after treatment

	T	df	P-Value	Mean value difference	Accuracy Span of test	
					Upper Limit	Lower Limit
Before treatment	8.005	9	0.000	68.50	87.85	49.14
After treatment	4.156	9	0.002	31.60	48.79	13.40

Discussion

There are various causes for microscopic hematuria in children. The most common causes include benign familiar hematuria, hypercalciuria, immunoglobulin A (IgA) nephropathy, sickle cell traits, anemia, and complications due to renal transplant. Less common causes include Alport's nephritis, post-infectious glomerulonephritis, trauma, exercise, renal stones, and Henoch-Schonlein purpura. Certain drugs and toxins (e.g. aspirin, sulfonamide, lead, etc.), coagulopathies, UTIs, tuberculosis, tumors, vascular malformations, structural anomalies, any form of glomerulonephritis, and lupus nephritis may occasionally cause microscopic hematuria [3]. In our study, all patients had a normal renal function without hypertension and proteinuria. The prevalence of microalbuminuria was 14.5% without any sex predominance. In a study by Assadi, urinary microalbumin excretion was assessed in 76 children with asymptomatic microscopic hematuria. All children underwent a percutaneous kidney biopsy to determine the cause of microalbuminuria. Twenty-two (29%) had microalbuminuria and 54 (71%) had normal albumin excretion. Of those with a normal level of albuminuria, 38 (70%) had normal renal tissue, 15 (28%) had thin glomerular basement membrane (TGBM) disease, and 1 (2%) had IgA nephropathy. In contrast, 20 (91%) of those with microalbuminuria had IgA nephropathy and 2 (9%) had TGBM disease [12].

Eardley et al reported 169 adult patients with microscopic hematuria who underwent renal biopsy. All participants had a normal serum creatinine level. Microalbuminuria was found in 52 (30%) patients, of whom 24 (48%) had IgA nephropathy, 23 (46%) had TGBM disease, 2 (4%) had other forms of glomerular disease, and 1 (2%) was histologically normal. Twenty-two of the 24 patients with IgA nephropathy were followed-up for 55 months of whom 5 developed overt proteinuria.

Of those with normoalbuminuria, 106 (89%) had TGBM disease or no glomerular abnormality, and 13 (11%) had IgA nephropathy of whom 12 were followed-up for a mean of 62 months and none developed overt proteinuria [13]. In these two studies, the prevalence of microalbuminuria was higher than our study, but renal biopsy and pathology assessment did not result in any additional diagnostic or therapeutic plan. Our children with microalbuminuria received AEC or ARB inhibitors that decreased microalbuminuria.

In these two studies, the most common renal pathology was thin glomerular basement membrane disease (TGBM). Since TGBM disease is a common cause of microscopic hematuria and is an autosomal dominant disorder, it has been argued that when evaluating a patient with microscopic hematuria, the family members of the index case should be screened for the presence of hematuria before beginning to do costly and invasive evaluations. TGBM disease is usually thought to have a good prognosis, with a very low risk of hypertension, proteinuria, or progressive renal failure. Renal biopsies rarely yield any additional information that can be used to manage children with isolated microscopic hematuria, except for those with documented episodes of gross hematuria or those who have close relatives with a history of hematuria or hypertension, edema, oliguria, significant proteinuria (> 500 mg/24 hours), or RBC casts in the urine [14]. Long term prognosis is unclear, particularly because a significant proportion of the patients is likely to have IgA nephropathy which can progress to end stage renal failure in 20% of them over 20 years [15].

Conclusions

Microscopic hematuria is a benign disease in children. Fallow-up with consideration of microalbumin/cr in random morning urine samples and evaluation of blood pressure and renal function tests is recommended. We believe that renal biopsy is not a *necessary* procedure in children with asymptomatic microscopic hematuria. Microalbuminuria screening test in children with asymptomatic microscopic hematuria is recommended.

Conflict of Interest

None declared

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None declared

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