ARTICLE

The Clinical Significance of Asymptomatic Gross and Microscopic Hematuria in Children

Jerry Bergstein, MD; Jeffrey Leiser, MD, PhD; Sharon Andreoli, MD

Background: The development of asymptomatic gross or microscopic hematuria is relatively common in children.

Objective: To evaluate the clinical importance of hematuria in children and the necessity for such an evaluation using a defined diagnostic protocol.

Design: The protocol included a personal and family history, physical examination and blood pressure determination, and a set of comprehensive laboratory and radiological examinations.

Results: Of 342 children with microscopic hematuria, no cause was uncovered in 274 patients. The most common cause discovered was hypercalciuria (16%), followed by post–streptococcal glomerulonephritis (1%). Of 228 children with gross hematuria, no cause was uncovered in 86 patients. The most common cause discovered was hypercalciuria (22%). Ten patients had clinically important structural abnormalities. Fifty-three patients qualified for renal biopsy; 36 had IgA nephropathy.

Conclusions: Our results suggest that diagnostic evaluation for potential causes of asymptomatic microscopic hematuria in children may not be necessary. Because microscopic hematuria can, rarely, be the first sign of occult renal disease, long-term follow-up is mandatory. As clinically important abnormalities of the urinary tract are commonly discovered in children with asymptomatic gross hematuria, a thorough diagnostic evaluation is warranted.

Arch Pediatr Adolesc Med. 2005;159:353-355

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-aged children has been estimated at 0.5% to 2.0%.[1,2] Traditionally, the detection of gross or persistent microscopic hematuria has prompted a thorough evaluation for causation.[3-5] However, the clinical significance of asymptomatic hematuria is unclear and the merit of such an evaluation has not been confirmed. In hopes of understanding these issues, we began a long-term prospective study using a defined protocol to evaluate children referred to our clinic for asymptomatic hematuria. This report summarizes our findings.

METHODS

This study was approved by the institutional review board of the Indiana University School of Medicine, Indianapolis. Between May, 1979, and May, 2002, 582 children were referred to our center for evaluation of asymptomatic gross or microscopic hematuria. Twelve patients were eliminated from further consideration because of a confirmed family history of hematuria, leaving a study group of 570 children. Microscopic hematuria was detected by the primary care physician in a random urine specimen obtained at the time of a periodic health examination and confirmed by a microscopic examination of the urine sediment showing more than 5 red blood cells per high-power field.

For editorial comment see page 398

Our evaluation consisted of a personal (to exclude antecedent upper respiratory tract infection, urgency, frequency, dysuria, flank or abdominal pain, rash, joint swelling, and edema) and family history, physical examination and blood pressure determination (reference ranges from the Task Force data tables[6]), and the following studies: complete blood count; urinalysis; serum creatinine and C3 levels; timed urine collection for calculation of the creatinine clearance (normal, >80 mL/[min · 1.73 m^2]), protein (normal, <150 mg/24 h), and calcium (normal, <4 mg/[kg · 24h]) excretions; and ultrasonography or intravenous pyelography. After 1981, ultrasonography became the study of choice. However, many referring physicians continued to perform intravenous pyelography, and those results are included in the data. In patients unable to contribute a timed urine collection, a random urine was obtained. Proteinuria was estimated by dipstick reaction (normal indicated by negative and trace readings) or the pro-

Author Affiliations:
Department of Pediatrics, Indiana University School of Medicine, Indianapolis.

Table 1. Number of Patients Having Discretionary Studies

Study	Microscopic Hematuria (n = 342)	Gross Hematuria (n = 228)
Antistreptolysin O or Streptozyme titer	153	126
Antinuclear antibody	109	102
Hemoglobin electrophoresis	21	16
Urine culture	215	158
Ultrasonography	180	111
Ultrasonography and intravenous pyelography	14	22
Ultrasonography, intravenous pyelography, and cystogram	12	8
Intravenous pyelography and cystogram	28	16
Intravenous pyelography	69	53
Ultrasonography and cystogram	39	18
Renal biopsy	2	53

Table 2. Demographic Characteristics of Children With Hematuria

Characteristic	Microscopic Hematuria	Gross Hematuria
No. of patients	342	228
Sex, M:F	165:177	161:67
White	316	210
African American	21	16
Asian American	5	2
Mean age at onset of hematuria, mo	78	104
Range	1-220	1-229
Mean age at first clinic visit, mo	91	111
Range	2-216	3-230

tein-creatinine concentration ratio (normal, <0.2) and calcium excretion by the calcium-creatinine concentration ratio (reference ranges from Sargent et al[7]). Serologic studies included an antistreptolysin O or Streptozyme titer, when the hematuria was of less than 6 months' duration, and an antinuclear antibody assay in teenaged patients. A hemoglobin electrophoresis was performed in all African American children. Urine cultures and additional radiological studies were performed at the discretion of the referring physician (**Table 1**). Indications for renal biopsy included (1) persistent high-grade (>100 red blood cells per high-power field) microscopic hematuria; (2) microscopic hematuria plus the later development of hypertension, decreased renal function, or proteinuria exceeding 150 mg/24 h; and (3) a second episode of previously unexplained (by evaluation of the first episode) gross hematuria.

RESULTS

MICROSCOPIC HEMATURIA

Three hundred forty-two patients were evaluated for microscopic hematuria (**Table 2**). In 274 patients (80%), no cause for the hematuria was uncovered (**Table 3**). The most frequent cause detected (16% of patients) was hypercalciuria in the absence of stone disease. Interestingly, 20% of these patients had a family history of stone disease. One patient had hypercalciuria and nephrolithiasis. Post–streptococcal glomerulonephritis (as defined by microscopic hematuria, a positive serum test result for streptococcal antibodies, and a low C3 level, all of which returned to normal within 3 months) occurred in 4 patients. Forty-five of 153 patients studied had elevated serum levels of streptococcal antibodies whereas none of 109 patients had antinuclear antibodies. Four patients had structural abnormalities of the urinary tract (2 had duplex collecting systems, 1 had a solitary kidney, and 1 had a unilateral hypoplasia). Two patients underwent kidney biopsy. One had persistent high-grade microscopic hematuria; the biopsy showed IgA nephropathy. The second had microscopic hematuria and a persistently low C3 level; the biopsy showed membranoproliferative glomerulonephritis.

Table 3. Evaluation Outcomes

Diagnosis	Microscopic Hematuria (n = 342)	Gross Hematuria (n = 228)
No diagnosis	274	86
Hypercalciuria without nephrolithiasis	56	51
Hypercalciuria with nephrolithiasis	1	2
IgA nephropathy	1	34
Post–streptococcal nephritis	4	21
Exercise	0	8
Thin basement-membrane disease*	0	3
Alport syndrome	0	3
Sickle cell trait	0	3
Mesangial proliferative nephritis	0	3
Autosomal dominant polycystic kidney disease	0	3
Membranoproliferative nephritis	1	2
Ureteropelvic junction obstruction	0	2
IgA nephropathy and hypercalciuria	0	2
Bilateral dysplasia	0	2
Urinary tract infection	0	1
Solitary kidney	1	1
Wilms tumor	0	1
Duplex collection system	2	0
Unilateral hypoplasia	1	0
Vesicoureteral reflux (grade 3)	1	0

*A relatively benign familial disorder characterized by hematuria, minimal proteinuria, normal renal function, and uniformly thinned glomerular basement membranes that may have links to Alport syndrome.[8]

GROSS HEMATURIA

Two hundred twenty-eight patients were evaluated for asymptomatic gross hematuria (Table 2). In 86 patients (38%), no cause for the hematuria was uncovered (Table 3). The most frequent (22%) cause detected was hypercalciuria in the absence of stone disease. Twenty-four percent had a family history of stone disease. Two patients had hypercalciuria with nephrolithiasis. Twelve patients had hypertension, 10 with glomerulonephritis and 2 with structural abnormalities. Fifty-three patients underwent kidney biopsy (Table 3). The majority had IgA nephropathy (67%) or post–streptococcal glomerulonephritis (11%). An additional 15 patients had post–streptococcal glomerulonephritis as defined by laboratory studies and clinical course (vide supra). Ten patients had clinically significant structural abnormalities: auto-

somal dominant polycystic kidney disease (3 patients), ureteropelvic junction obstruction (2 patients), kidney stones (2 patients), bilateral renal dysplasia (2 patients), and Wilms tumor (1 patient).

COMMENT

Our results indicate that asymptomatic microscopic hematuria in children is rarely associated with clinically important disease of the urinary tract. No cause was found in the large majority of patients. The most common cause discovered was hypercalciuria (16% of patients) followed by post–streptococcal glomerulonephritis (1%).

Our data suggest that a diagnostic evaluation for potential causes of microscopic hematuria in children may not be necessary. Although children with hypercalciuria may be at long-term risk for the development of nephrolithiasis[9] and bone demineralization,[10] there are no long-term follow-up studies demonstrating that early detection is beneficial in preventing these potential risks. As asymptomatic post–streptococcal glomerulonephritis resolved spontaneously and without complication in all 4 patients, detection seems unnecessary.

Interestingly, not one patient with microscopic hematuria had evidence of urinary tract infection, a commonly sought cause of hematuria. This militates against including a urine culture in the evaluation of asymptomatic patients.

We found clinically insignificant abnormalities in the upper urinary tracts of 5 of 342 children and grade 3 reflux in 1 of 79 patients. The absence of clinically important radiological abnormalities in children with microscopic hematuria is supported by the findings of Feld et al.[11] In their study, renal ultrasonography examinations of 283 children showed only 18 clinically insignificant abnormalities. Of 90 voiding cystograms, 9 showed low-grade reflux (grades 1 or 2). Thus, in children with asymptomatic microscopic hematuria, radiological studies fail to reveal abnormalities requiring clinical intervention.

Although not specifically evaluated in this study, routine renal biopsy seems unwarranted in children with microscopic hematuria. Vehaskari et al[2] took biopsy samples from 22 children with microscopic hematuria having no family history of kidney disease and a negative evaluation for causation. Two patients had IgA nephropathy and 1 had probable Alport syndrome. The remaining biopsy results were normal or showed nonspecific focal tubular changes that the authors deemed insignificant. Trachtman et al[12] performed biopsies on 42 children with microscopic hematuria after a similar negative evaluation. Thirty biopsy results were normal, 10 showed thinning of the glomerular basement membranes, 1 showed IgA nephropathy, and 1 showed Alport syndrome.

Rarely, asymptomatic microscopic hematuria can be the first sign of occult renal disease. However, it seems likely that in patients with microscopic hematuria due to occult glomerular disorders, progression to clinically significant disease will be accompanied by the development of hypertension and/or proteinuria. Thus, long-term follow-up of children with microscopic hematuria is mandatory. We recommend a blood pressure measurement and urinalysis at the time of the annual physical examination. The development of hypertension and/or proteinuria or the onset of gross hematuria mandates a thorough reevaluation and consideration of kidney biopsy.

On the other hand, a clinically important cause for gross hematuria was much more common. The most frequent causes included hypercalciuria (23% of patients), IgA nephropathy (16%), and post–streptococcal glomerulonephritis (9%). As in microscopic hematuria, urinary tract infection was a very rare cause of gross hematuria, occurring in only 1 patient. These results suggest that a thorough evaluation for underlying causation remains important in children with gross hematuria.

An important limitation of our study is the absence of long-term follow-up. Patients with unexplained hematuria were returned to their primary care physician with the recommendation to monitor the child for the development of hypertension, decreased renal function, proteinuria, or a second episode of gross hematuria. The rate of compliance with this recommendation and the frequency of the subsequent development of occult kidney disease are unknown. That not one patient with microscopic hematuria returned for reevaluation supports the hypothesis that this is a benign disorder.

In summary, our results suggest that asymptomatic microscopic hematuria in children is rarely associated with clinically significant disease of the urinary tract and may not warrant diagnostic evaluation. However, long-term follow-up is mandatory. As asymptomatic gross hematuria is more commonly associated with urinary tract disease, a thorough evaluation for causation is justified.

Accepted for Publication: October 11, 2004.
Correspondence: Jerry Bergstein, MD, James Whitcomb Riley Hospital for Children, 699 West Dr, Room 213, Indianapolis, IN 46202-5119 (jbergste@iupui.edu).

REFERENCES

1. Dodge WF, West EF, Smith EH, Bunce H. Proteinuria and hematuria in school children: epidemiology and early natural history. *J Pediatr*. 1976;88:327-347.
2. Vehaskari VM, Rapola J, Koskimies O, Savilahti E, Vilska J, Hallman N. Microscopic hematuria in schoolchildren: epidemiology and clinicopathologic evaluation. *J Pediatr*. 1979;95:676-684.
3. Brewer ED, Benson GS. Hematuria: algorithms for diagnosis, I: hematuria in the child. *JAMA*. 1981;246:877-880.
4. Fogazzi GB, Ponticelli C. Microscopic hematuria diagnosis and management. *Nephron*. 1996;72:125-134.
5. Cruz CC, Spitzer A. When you find protein or blood in the urine. *Contemp Pediatr*. 1998;15:89-109.
6. National Heart, Lung, and Blood Institute. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure Education Program. *Pediatrics*. 1996; 98:649-658.
7. Sargent JD, Stukel TA, Kresel J, Klein RZ. Normal values for random urinary calcium to creatinine ratios in infancy. *J Pediatr*. 1993;123:393-397.
8. Savige J, Rana K, Tonna S, Buzza M, Dagher H, Wang YY. Thin basement membrane nephropathy. *Kidney Int*. 2003;64:1169-1178.
9. Stapleton FB. Hematuria associated with hypercalciuria and hyperuricosuria: a practical approach. *Pediatr Nephrol*. 1994;8:756-761.
10. Polito C, Iolascon G, Nappi B, Andreoli S, La Manna A. Growth and bone mineral density in long-lasting idiopathic hypercalciuria. *Pediatr Nephrol*. 2003;18:545-547.
11. Feld LG, Meyers KEC, Kaplan BS, Stapleton FB. Limited evaluation of microscopic hematuria in pediatrics. *Pediatrics*. 1998;102:E42.
12. Trachtman H, Weiss RA, Bennett B, Greifer I. Isolated hematuria in children: indications for a renal biopsy. *Kidney Int*. 1984;25:94-99.