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Review Article

Etiology of Hematuria in Children: A Review Article

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ABSTRACT

Background and Aim: The etiology of hematuria in children is different. Hematuria is a known risk factor for developing chronic kidney disease (CKD). This narrative review aimed to evaluate the etiology of hematuria in children, mainly new hematuria research, to provide an update on the management, and complications that can improve the prognosis of hematuria.

Methods: For this narrative review, articles from several sources, including Scopus, Google Scholar, Embase, Web of Science, PubMed, and the Directory of Open Access Journals were used.

Results: Kidney and urinary tract infection (UTI) is the most common cause of hematuria in children. Renal structural abnormalities, hypercalciuria, urinary stones, and extrarenal abnormalities associated with hematuria.

Conclusion: Hematuria is a symptom and very dangerous, but due to various causes in these patients, it is needed in all patients.

The challenge for pediatric nephrologists is the early diagnosis of children with progressive forms of kidney disease from other causes. This manuscript reviews the multiple potential causes of microscopic hematuria and provides a framework for the initial assessment and monitoring of such patients. No internationally accepted, uniform, evidence-based algorithm exists for its diagnostic evaluation anywhere. It is recommended that extensive public attention be paid to the etiology and management of hematuria.

Keywords: Hematuria, Urinary tract infection (UTI), Chronic kidney disease (CKD)

Introduction

Learning objectives

At the end of undergraduate medical training, the learner will be able to:

Define macroscopic and microscopic hematuria.

Explain the methods of microscopic examination of urinalysis to detect blood in the urine.

Discuss methods of evaluating hematuria.

Identifying risk factors that increase the likelihood of malignancy in the urinary tract, during the evaluation of hematuria.

In the evaluation of hematuria, identification of risk factors that increase the possibility of progressive forms of kidney disease from other causes in the urinary system.

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Explanation of symptoms of the nephritic syndrome, such as rise in blood urea nitrogen (BUN) and creatinine (Cr), red blood cell cast, hypertension, and edema in patients with microscopic hematuria.

Hematuria is defined as the persistent presence of more than 5 red blood cells (RBC)/µL in a fresh uncentrifuged midstream urine specimen and greater than 3 RBC/high-power field in centrifuged sediment from 10 mL of freshly voided midstream urine [1-3].

The prevalence of microscopic hematuria in the community is between 1.7% and 31.1%, but it depends upon age, sex, and other factors. In the study of the prevalence of hematuria in school children, 0.5 to 6% of them have hematuria, and at least one-third of them continue for more than 6 months [1, 2, 3]. Persistent hematuria is defined as positive urine analysis (UA) more than 4 -6 weeks in the absence of menses, exercise activity, or trauma [3]. Evaluation of persistent hematuria with or without proteinuria by renal biopsy identified glomerulonephritis as a cause in 25.4%–52.3% [1]. Increasing evidence shows that persistent hematuria, particularly if associated with proteinuria, is a risk factor for chronic kidney disease (CKD) in the longer term [1, 4]. High-risk patients include those with gross hematuria or those with invisible hematuria and risk factors [1, 2, 4].

Isolated microscopic hematuria has a good renal outcome, but the lifetime risk of CKD may be higher in certain patients, depending on the specific underlying disease [3]. Asymptomatic patients with isolated microscopic hematuria should not undergo extensive diagnostic measurement. A child with completely asymptomatic isolated microscopic hematuria that persists in at least three urine tests observed over at least a 2-week period should undergo detailed diagnostic testing. A significant urinary tract disease with this clinical presentation is rare. A child with hematuria is evaluated by a detailed history, physical examination, microscopic examination of urine, family history, and identification of anatomical anomalies, anomaly syndromes, hypertension (HT), edema, and heart failure [1-6]. In the initial assessment of a child with hematuria, detailed family history is critical given the multiple genetic causes of renal disorders. Kidney and urinary tract bacterial infection is the most common cause of hematuria in children [1, 2]. Recurrent episodes of gross hematuria suggest Alport syndrome, IgA nephropathy, or thin glomerular basement membrane disease [1, 2, 7]. Blood or RBCs can enter the urine at multiple anatomical sites and mix with the urine. These include the urinary system, female reproductive system, and integumentary system. Urinary causes occur anywhere between the kidney and the urethral meatus [3]. The timing of gross hematuria can also provide critical clues regarding the etiology. For instance, bleeding noted before or at the beginning of the urine stream is likely to originate from the urethra, whereas midstream or late-stream gross hematuria is likely to originate higher in the genitourinary tract [2, 6]. Some methods to detect hematuria are microscopic, macroscopic, and dipstick method. Macroscopic hematuria is visible, microscopic hematuria is invisible to the eye. The presence of at least 1 mm of blood per liter of urine can cause a visible color change, and 2 to 3 RBCs per high-power field (HPF) can make the urine dipstick positive [3, 5].

The dipstick method is also used to diagnose microscopic hematuria. The urine dipstick tests for the peroxidase activity of hemoglobin (or myoglobin); thus, a dipstick that is positive for blood is positive to detect RBCs, hemoglobinuria, or myoglobinuria in the urine. Dipsticks have a sensitivity of 95% and a specificity of 75% and positive results should be confirmed with a microscopic examination of the urine because patients may test positive when true blood is not present [3, 5]. A false negative dipstick result can be caused by the ingestion of high doses of vitamin C [2, 5]. Free hemoglobin, myoglobin, and certain antiseptic solutions (povidone-iodine) cause these false positive readings [1, 8]. Knowing the serum myoglobin level and results of the microscopic urinalysis helps to differentiate these confounders. The presence of many epithelial cells suggests skin or vaginal contamination. Microscopic examination of urine is performed on 10 mL of a midstream, clean-catch specimen that has been centrifuged for 10 minutes at 2000 rpm or for 5 minutes at 3000 rpm. The sediment is resuspended and examined under high-power magnification. Hemoglobin or myoglobin in urine without RBCs causes heme-positive urine. Hemolysis can cause hemoglobinuria without hematuria. In rhabdomyolysis, myoglobinuria occurs without hematuria [2]. Upper urinary tract sources of hematuria originate within the nephron (glomerulus, tubular system, or interstitium). These can be divided into non-glomerular and glomerular causes [1]. The causes of glomerular hematuria in children are more common than the causes of the lower tract of hematuria and common causes include thin glomerular basement membrane disease, IgA nephropathy, hereditary nephritis (Alport›s disease), glomerulonephritis and benign familial hematuria, [9-15]. Non-glomerular causes can be further subdivided into the lower urinary tract and upper urinary tract causes [1, 2]. Cases of the upper urinary tract include hypercalciuria, urinary stones, pyelitis, pyelonephritis, structural disorders of the kidney, and cancer [16-20]. Glomerular hematuria is

often associated with brown, tea-colored, or burgundy urine, proteinuria >100 mg/dL via dipstick, urinary microscopic findings of RBC casts, and large numbers of dysmorphic red blood cells, or more than 5% acanthocytes [5, 6]. Intraglomerular hematuria is often associated with brown, tea-colored, or wine-colored urine, proteinuria >100 mg/dL, red blood cells, and large numbers of misshapen red blood cells or more than 5% acanthocytes [1, 5]. Tubular hematuria may be associated with the presence of leukocytes or renal tubular casts [1, 5]. Lower urinary tract cases include kidney or urinary cancer, urinary tract infection (UTI), and vigorous exercise. Lower urinary tract sources of hematuria originate from the pelvocaliceal system, ureter, bladder, or urethra [1, 2] and it may be associated with gross bright red or pink hematuria, terminal hematuria (gross hematuria occurring at the end of the urine stream), blood clots, normal urinary RBC morphology, and minimal proteinuria on dipstick [2, 4]. After conducting a thorough history and physical examination, further medical testing is necessary. Patients can be stratified into high-risk and low-risk categories [1]. High-risk patients include those with visible hematuria or those with invisible hematuria and risk factors [5]. A complete consideration of the urinary tract is indicated for hematuria. This includes imaging of the upper urinary tract and urinary causes occur anywhere between the kidney glomerulus and the urethral meatus [1, 2]. An increasing role for genetic testing is observed in children with hematuria, particularly where a family history of hematuria, deafness, or CKD exists [1, 9]. Imaging (ultrasound and spiral CT scan without contrast) is vital if urolithiasis or a structural abnormality is suspected [1]. The causes of hematuria can be recognized according to its temporary nature and related symptoms.

Upper urinary tract hematuria

Glomerular hematuria may indicate glomerular filtration barrier dysfunction or damage [9]. Recent studies suggest that glomerular hematuria may be a negative prognostic factor for renal function outcome [9, 12]. Approximately 10% of children with gross hematuria have an acute or chronic form of Glomerulonephritis (GN), which can be part of an associated systemic disease [9, 12]. The presence of edema, painless microscopic hematuria, flank pain, or signs of heart failure suggests acute GN. Diseases commonly manifesting as GN include granulomatosis with polyangiitis, microscopic polyarteritis nodosa, postinfectious GN, Immunoglobulin A (IgA) nephropathy, goodpasture syndrome, systemic lupus erythematosus (SLE) nephritis membranoproliferative GN (MPGN), henochhönlein purpura (HSP) nephritis, and hemolytic-uremic syndrome (HUS) [9, 10, 12]. In immunoglobulin (Ig) A nephropathy, severe hematuria occurs 1-2 days after the onset of a viral upper respiratory tract infection, but in acute post-infectious streptococcal glomerulonephritis (PSGN), hematuria after 7-21 day between the onset of streptococcal pharyngitis or a skin infection [9, 12, 17]. Worldwide, the most common chronic glomerular disease in children is IgA nephropathy [4]. It is characterized by a predominance of IgA within mesangial glomerular deposits in the absence of systemic disease [2]. A history of recent gastrointestinal infection suggests HUS. Skin rash and joint complaints suggest Henochhönlein Purpura (HSP) or SLE nephritis [2]. Hereditary glomerular diseases include hereditary nephritis (isolated Alport syndrome or with leiomyomatosis or macrothrombocytopenia), thin glomerular basement membrane disease, SLE nephritis, hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC), and IgA nephropathy (Berger disease) [9]. Hereditary hematuric renal diseases include atypical HUS, urolithiasis, both autosomal recessive (ARPKD) and autosomal dominant polycystic kidney diseases (ADPKD), and sickle cell disease/trait [2, 16, 18].

Lower urinary tract hematuria

The initial assessment of these children should include a urine culture followed by spot urine for calcium to creatinine ratio in culture-negative patients. In African-American patients, a sickle cell screen should be included. If these studies are normal, urinalysis of all first-degree relatives is indicated [1, 4, 6, 20]. Ultrasound of the kidney, urinary tract and bladder should be considered to rule out structural lesions, such as tumors, cystic diseases, hydronephrosis, or nephrolithiasis. Ultrasonography of the urinary tract is most informative in patients presenting with hematuria, abdominal discomfort, flank pain, or trauma. If these initial studies are normal, an assessment of serum creatinine and electrolytes is suggested. Hypercalciuria is seen in 26%–36% of children with gross or microscopic hematuria. Hypercalciuria is associated with a strong family history of urolithiasis [20], with a suggestion that it may have an autosomal dominant inheritance pattern [1, 4]. Frequency, dysuria, and fevers suggest a urinary tract infection (UTI), whereas renal colic suggests renal stone [16, 18]. A flank mass can suggest hydronephrosis, renal cystic diseases, renal vein thrombosis, mass, or tumors. Hematuria associated with headache, mental status changes, visual changes (diplopia), active bleeding or epistaxis, or heart failure suggests associated with severe hypertension (HT). Patients with hematuria and a history of trauma require immediate action [2]. Child abuse must always be suspected in the child presenting with unexplained perineal bruising, rash, and hematuria [1].

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A flank mass can suggest hydronephrosis, renal cystic diseases, renal vein thrombosis, or tumor. Hematuria associated with headache, mental status changes, visual changes, epistaxis, or heart failure suggests associated severe hypertension [2]. Patients with hematuria and a history of trauma require immediate evaluation. Dysuria and abdominal or flank pain are symptoms of idiopathic hypercalciuria, or urolithiasis [1, 21]. Urethrorrhagia, which is urethral bleeding in the absence of urine, is associated with dysuria and blood spots on underwear after voiding. This condition, which often occurs in prepubertal boys at intervals several months apart, has a benign self-limited course [1, 2]. This review article aims to present the different causes of hematuria in children along with recommendations from different guidelines of different medical societies. All potential causes of hematuria must be considered, and all individual risk factors considered to identify or rule out underlying disease requiring treatment. We recommend a basic diagnostic process, further diagnostic investigations based on risk, and monitoring for hematuria. This manuscript reviews the multiple potential causes of hematuria and provides a framework for the initial evaluation and monitoring of such patients.

Discussion

Hematuria is a very worrisome symptom, but considering that it is a risk factor for progression to renal failure, investigation of the cause is essential in all patients. The most common causes of gross hematuria are infections of the lower urinary tract, especially the bladder [1, 6]. The etiology of hematuria in children is different. This study is considered for some reasons. First, some causes of hematuria in children are genetic or congenital, but it is essential to discover, diagnose, monitor, and control their complications. Considering the types of heredity in these patients, a genetic study is necessary for the patient, parents, and family [6, 7]. In this study, we investigated the update of inheritance in hematuria. Secondly, however, hematuria is a known risk factor for the development of CKD [1-4, 7]. The challenge for pediatric nephrologist is to distinguish children with potentially progressive forms of kidney disease versus other causes while minimizing cost and inconvenience for the child and family. Third, no uniform, internationally accepted, evidence-based algorithm exists for its diagnostic evaluation anywhere. The strategy and the duration of monitoring patients are variable, and not based on solid evidence [3-6]. Authors' strategies and duration of ultrasound monitoring vary widely; controls of blood urinary nitrogen (BUN) and creatinine (Cr) every twelve months and urinary sediment (U/A) biannually [11]. Furthermore, even when spontaneous resolution is documented in the laboratory, there may be a risk of progression to chronic renal failure (CRF) and the patient should be monitored for a long time [21-23]. Fourth, it is recommended that extensive public attention be paid to the etiology and management of hematuria. Fifth, the improvement of early diagnosis and better care of these patients in the past years is due to the increased attention and skill of colleagues and the improvement of laboratory technology that is currently available. Sixth, considering extrarenal diseases that cause hematuria, it is essential to know these diseases and their long-term renal complications. Seventh, according to the current data and the increasing prevalence of kidney stones in children, in the diagnostic evaluation and monitoring of hematuria, if the ultrasound does not show structural abnormalities in the kidneys and bladder, considering the cost and side effects caused by radiation, computerized tomography of kidney and urinary system (CTU) should never be used [5].

Limitations of the study

Our study was conducted in one center. Our proposal is a wider, multicenter study of this issue and finding a uniform method to deal with hematuria in children.

Conclusion

According to the current findings, it is recommended to conduct further studies on the early diagnosis and long accurate management of this disorder, especially on prenatal awareness. Prospective multicenter collaborative studies are needed to develop guidelines, provide an evidence-based framework for family counseling and education, and clarify expectations for prenatal and postpartum engagement.

Ethical Considerations

Compliance with ethical guidelines

This is a review article with no human or animal samples.

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Authors' contributions

The principal investigator of the study: Mohammad Hoseinn Akhavan Sepahi; Participating in preparing the concept, design, and revision of the manuscript and criti-

cally evaluating the intellectual contents: The both authors. The authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflict of interest

The authors conducted the study based on the clinical experience of this rare disease to inform other clinicians. Therefore, the authors declare no conflict of interest.

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