Evaluation of hematuria and proteinuria: how should a pediatrician proceed?

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Purpose of review

Finding blood or protein in the urine of a patient can be the source of immense anxiety. The list of diseases that result in these findings is quite long. Thus, many pediatricians believe that an exhaustive investigation is necessary to be certain of the cause. The review will discuss the major causes of hematuria and proteinuria in the pediatric population, and discuss a rational approach to the evaluation of these conditions.

Recent findings

A number of recent studies have examined the results of mass screenings of school-age children and the final outcome of examination of children with hematuria and/or proteinuria. Most children with either isolated hematuria or isolated proteinuria had benign disease processes. Children with combined hematuria and proteinuria had a higher prevalence of significant kidney disease.

Summary

The urinalysis combined with the history and physical examination should indicate the cause of hematuria and proteinuria in most cases. Significant renal disease can be ruled out with a minimal amount of work-up in most patients. The presence of hematuria and proteinuria together significantly increases the likelihood of significant renal disease and should prompt a referral to a specialist.

Keywords

glomerulonephritis, orthostatic proteinuria, renal biopsy

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Introduction

Finding blood or protein in the urine can be the source of immense anxiety for the patient and family as well as for the pediatrician. As the list of diseases that result in these findings is quite long many pediatricians believe that an exhaustive investigation is necessary to be certain of the cause. For most patients, however, the work-up of hematuria and proteinuria is very straightforward, and can be pursued by the pediatrician. The current review will cover the basic information related to these topics and will help the pediatrician understand the answers to the questions that most parents will ask. The recommendations provided are supported by the results of a number of recent studies that review the results of mass screenings of otherwise asymptomatic children as well as follow-up of patients who have undergone renal biopsy.

Hematuria

The primary objective in the evaluation of the patient with hematuria is to determine whether or not they have significant renal disease. The differential diagnosis for hematuria is extensive, but can be narrowed by taking a careful history and performing a complete physical examination. This includes measuring the patient's blood pressure and plotting the child on a growth curve. Does the patient have gross or microscopic hematuria, flank pain or edema? Did the patient have a recent throat or skin infection? Does the patient have a rash, joint pain or swelling? A careful family history can also help reveal the cause of the findings. Are there family members with kidney stones or deafness? Routine questioning should also include whether or not there are family members on dialysis.

If the history and physical examination are unrevealing, the pediatrician must then determine if an extensive work-up should be initiated. The results of several recent studies are useful in determining the probability of significant disease in these asymptomatic patients. While the overall findings in these studies are similar, there were a few differences which can most likely be explained by the indications used for performing a biopsy.

In a thorough evaluation of a large population of children with abnormal urinalyses by Park *et al.* [1], over 7 million school children were screened by urinalysis. Of the 1044 that were found to have an abnormal urinalysis,

719 (60.1%) had isolated hematuria. Renal biopsy was performed in patients who had severe proteinuria, hypertension, abnormal renal function or a family history of renal disease. With these strict criteria, the likelihood of finding significant renal disease was high. Of the 719 patients with only isolated hematuria, 52 underwent renal biopsy. Thin basement membrane disease was found in 33 of these patients [1]. A total of 16 other patients had definable pathologic findings on the biopsy, such as IgA nephropathy.

Similar results were obtained in a study by Lee *et al.* [2••]. There were 461 children with abnormal urinalyses found through a school screening program who underwent further evaluation, including a renal biopsy. Renal biopsy was performed in patients who had hematuria for more than 6 months, heavy proteinuria or the combination of hematuria and proteinuria. Of the 289 with isolated hematuria, almost half (47.1%) had normal findings on the biopsy. The higher percentage of normal biopsy findings is most likely due to the lower threshold for performing a biopsy in this study as compared with the previous study. The most common pathologic diagnosis was thin basement membrane disease, followed by IgA nephropathy [2••].

The results of these two studies indicate that the two most common diagnoses found on biopsy were thin membrane disease and IgA nephropathy. Thin membrane disease is now thought to be a defect in the collagen type 4 gene and is synonymous with hereditary nephritis without deafness to distinguish it from Alport's disease [3,4]. The prognosis of this disease is generally favorable. IgA nephropathy, otherwise known as Berger's disease, also has a favorable prognosis for most patients, but there is a subset of patients who do not do very well [5,6]. The treatment for IgA nephropathy is not entirely clear, but most nephrologists would use fish oil and an angiotensin converting enzyme inhibitor [7,8].

Another recent study by Chandar *et al.* [9] reviewed 239 patients who had abnormal urinalyses but had no symptoms of renal disease (e.g. urinary tract infection). Of the 109 patients noted to have isolated microscopic hematuria, the most common diagnosis was hypercalciuria and only five patients had significant renal disease [9]. In approximately half of the patients, no diagnosis was found and 30% of the patients were found to have hypercalciuria [9].

The results of a study by Bergstein *et al.* [10] also showed similar results. Of the 342 children who had only microscopic hematuria, no diagnosis was found in 274. The most common cause that was elucidated was hypercalciuria in about 16% of the patients [10]. This study was accompanied by an editorial review which concluded that minimal evaluation is required in asymptomatic patients who have isolated microscopic hematuria [10].

An older study by Feld *et al.* [11], which focused primarily on the diagnosis of hypercalciuria, had similar findings. Out of 325 patients with isolated hematuria, 29 patients had hypercalciuria. None of the patients in this study underwent renal biopsy. As a result of their findings, the authors advocated minimal work-up of asymptomatic patients with isolated hematuria [11].

Gross hematuria

The findings with gross hematuria are somewhat different from the studies outlined above for microscopic hematuria. A review of 10 years of experience in a urology clinic revealed that most patients seen had benign diseases [12]. These patients were referred to the urologist, so it is not clear how much of a medical work-up was performed prior to the evaluation by the urologist. These authors reviewed 342 patients who had presented with gross hematuria. Of the 272 males, 52 (19%) had benign urethrorrhagia [12]. Other findings included urinary tract infections, trauma and stones. Remarkably, there were three patients with low-grade transitional cell carcinoma and one patient with Wilms tumor. Overall, the authors concluded that most of the patients had a benign disease and did not warrant cystoscopy [12].

A study that was reported by pediatric nephrologists found that, out of 82 patients presenting with gross hematuria, 24 had glomerular disease [13]. Of the remaining 56 patients with nonglomerular hematuria, the most common finding was hypercalciuria [13]. Other diagnoses included urethrorrhagia and hemorrhagic cystitis. Interestingly, there were 26 patients (32%) who had no diagnosis [13].

In the study by Bergstein *et al.* [10], 228 patients were found with gross hematuria. They also found no cause of the hematuria in about 37.7% (86 patients). The most common cause that was found was hypercalciuria. Other causes included IgA nephropathy, post-streptococcal glomerulonephritis and autosomal dominant polycystic kidney disease [10].

Evaluation of hematuria

The studies discussed above give some guidance as to the work-up of a patient presenting with hematuria. The problem remains, though, that the patient populations reported in these studies might not accurately represent a particular patient whom the pediatrician is assessing. The studies that were based on school screening programs yield information that applies to asymptomatic patients.

The patient in the pediatrician's office has, however, probably presented with some complaint. As mentioned above, a careful history and physical examination should provide clues to guide the initial evaluation of the patient. The evaluation outlined here is very similar to one that is outlined in a recent publication by the Indian Pediatric Nephrology Group [14].

As microscopic hematuria can be transient, the urinalysis should be repeated several times over a period of days to weeks. If the urine is red, the pediatrician should obtain a microscopic evaluation of the urine to be certain that the patient indeed has hematuria. There are other causes of red urine besides hematuria (see Table 1) [14,15]. Once it is established that the patient has persistent hematuria, an initial work-up should be done.

Some routine initial tests that will most likely be done for most patients are a renal sonogram, renal function tests (blood urea nitrogen and creatinine) and basic serologies (e.g. antinuclear antibodies, C3, etc.). While the above studies indicate a low yield for the renal sonogram, it is a noninvasive study that can provide some reassurance to an anxious family that there are no major structural problems or tumors in the kidney. Once these tests have been done, additional work-up will be dictated by the initial findings and the suspicion for the disease. The goal of this evaluation is to determine if the patient has significant renal disease that might progress to chronic kidney disease.

The above studies indicate that patients with isolated microscopic hematuria have a high probability of having a benign condition. Since one of the most common findings was hypercalciuria, it is reasonable to check the urine calcium excretion. This is done by measuring the urinary calcium and creatinine in milligrams per deciliter. Many labs will report the calcium in other units, so a unit conversion might have to be done. The normal range for children is less than 0.21 [16]. Younger infants will have a higher normal value [17]. For example, infants under 7 months have a ratio of 0.86. This then decreases with age so that children between 19 months and 6 years have a ratio of about 0.42 [17]. While the calcium to creatinine ratio can be more easily obtained, the 24-h excretion of calcium is a more accurate method of determining hypercalciuria [16].

Table 1 Causes of red urine without hematuria[a]

Drugs
Chloroquine
Ibuprofen
Iron sorbitol
Nitrofurantoin
Phenazopyridine
Phenolphthalein
Foods
Beets
Blackberries
Food coloring
Metabolites
Bile pigments
Homogentisic acid
Melanin
Methemoglobin
Porphyrin
Tyrosine
Urates

[a] Adapted from [8,9].

Another key question to answer is whether the hematuria is of glomerular or nonglomerular origin [14]. There have been many attempts to find a quick and easy way to make this determination; however, the single best test remains a careful urine examination by the physician. Finding red blood cell casts in the urine is the hallmark of a glomerular source for hematuria. In the absence of red blood cell casts, a high proportion of dysmorphic red blood cells (acanthocytes) in the urine is highly suggestive of glomerulonephritis [14]. A phase contrast microscope is needed to distinguish acanthocytes. Other methods for determining this include measuring the cell size distribution of the red cells in the urine. As the dysmorphic cells are smaller, this can be determined using a cytometer [18]. Unfortunately, this methodology is usually not readily available.

Another approach has been to examine the protein in the urine. A recent study suggests that the character of the protein in the urine will help determine the source of the bleeding [19]. The urinary albumin to total protein ratio was used to determine if the hematuria was glomerular or nonglomerular in origin. The authors found that patients with a urinary albumin to total protein ratio of greater than 0.59 had a very high likelihood of having glomerular disease. While this approach is novel and might be useful, it will require further studies to establish its usefulness clinically.

Proteinuria

There are a number of issues to consider in the evaluation of proteinuria. First, the protein excretion needs to be quantified. The gold standard remains a 24-h urine collection for protein excretion. Drawbacks include the fact that this is inconvenient and the patient might not perform a complete collection. For many pediatric patients, the protein excretion can be quantified using a random urine sample and measuring the protein to creatinine ratio. A number of studies in children and adults show very good correlation between the protein to creatinine ratio and the total protein excretion [20–22]. A few recent studies have pointed out some problems with this technique so again, the 24-h urine collection remains the gold standard [22].

An excellent review for the evaluation of the pediatric patient with proteinuria shows that normal excretion of

protein is less than 4 mg/m^2/h on a 24-h urine sample or less than 0.2 when assessing the urine protein to creatinine ratio [23]. The units of both protein and creatinine should be in milligrams per deciliter for this value. The excretion of greater than 40 mg/m^2/h on a 24-h urine sample or greater than 2 when assessing the urine protein to creatinine ratio is consistent with nephrotic syndrome [23].

The next consideration is the fact that orthostatic proteinuria is a very common cause of protein excretion in growing children and adolescents [24]. The incidence is very high in the pubertal child. This can be determined by performing a split urine collection. It is critical that this be done by the patient's position (upright vs. supine) and not by 12-h increments of the clock. Another approach is to measure the protein to creatinine ratio in the first morning urine [23].

The last consideration in the evaluation of proteinuria is the assessment of the type of protein in the urine. Since the glomerulus usually filters some protein that is reabsorbed by the proximal tubule, the protein in the final urine can be the result of increased protein being filtered or a decrease in the tubular reabsorption of protein [25,26]. While this could be an important clue in determining the cause of the proteinuria, it requires testing for specific proteins in the urine and is not available on routine dipstick testing. Diseases such as Dent's disease or Lowe's syndrome have tubular proteinuria.

Evaluation of proteinuria

As with the evaluation of hematuria, a careful history and physical examination are pivotal [23]. Does the patient have significant edema, indicating the nephrotic syndrome? Are there other signs or symptoms indicating systemic disease? Is the proteinuria persistent or orthostatic? The initial evaluation would include most of the same tests that were indicated for hematuria. It is not clear if a sonogram is beneficial in the work-up of isolated proteinuria. There are scant data to determine its role; however, anecdotal evidence would suggest that it should be considered.

Hematuria and proteinuria

While isolated hematuria and isolated proteinuria in general have a benign course, the finding of combined hematuria and proteinuria is more suggestive of significant renal disease. In the study by Park *et al.* [1], the biopsy results for patients with combined hematuria and proteinuria had a higher incidence of IgA nephropathy compared with those with isolated hematuria. In the study by Lee *et al.* [2••], the findings were similar. The combination of hematuria and proteinuria resulted in more patients having significant renal disease than those with isolated hematuria [2••]. Chandar *et al.* [9] reported a similar increase in the incidence of significant renal disease in this group of patients. Thus, the patient with combined hematuria and proteinuria will probably need referral to a pediatric nephrologist for a complete work-up, which might include a renal biopsy.

Biopsy

One of the key questions the parents might have in the work-up of a patient with hematuria or proteinuria is if and when to do a renal biopsy. As discussed above, if the patient has isolated hematuria, the likelihood that a biopsy is indicated is remote. If the patient has isolated proteinuria that is not in the nephrotic range, the likelihood might be higher. This would depend on the history and physical examination, and whether or not there is a concern that the patient could have a progressive disorder such as focal and segmental glomerulosclerosis [23]. It should be noted that many cases of proteinuria in children are transient or orthostatic in nature and do not require a biopsy. If the patient has both hematuria and proteinuria, the likelihood of needing a biopsy is much greater. Fortunately, renal biopsy in pediatrics has become very routine and is safe [27].

Conclusion

While the finding of isolated hematuria or proteinuria can be very alarming to the patient and the family, the data indicate that most patients have a benign disease. A careful history and physical examination as well as a minimal work-up can determine if there is significant renal disease. The algorithm presented by the Indian Pediatric Nephrology Group provides a detailed guide to the work-up of hematuria [14]. A more extensive set of algorithms can be found in a report in Health Technology Assessment; however, this report is primarily for adult patients [28••]. The work-up of proteinuria in pediatrics has been outlined in the journal *Pediatrics* [23]. The combination of hematuria and proteinuria indicates a much higher risk of significant renal disease. In these patients, the pediatrician should have a low threshold for referral to a pediatric nephrologist.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 223–224).

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