ASYMPTOMATIC HEMATURIA AND PROTEINURIA

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Microscopic hematuria or proteinuria, or both of these together are occasionally detected in apparently healthy, asymptomatic children, and pose diagnostic problems. In a majority of such children, presence of abnormal number of red blood cells (RBC) or small amounts of protein may not indicate a serious renal disorder. A detailed clinical and a minimum laboratory evaluation should nevertheless be carried out.

Urine Examination

Repeated meticulous urinalyses are essential to confirm urinary abnormalities. The specimen should be fresh and concentrated (specific gravity ≥1020). The first specimen passed in the morning is usually suitable. Protein is estimated with heat coagulation test, sulfosalicylic acid precipitation or the dipstick method, and expressed on a semi-quantitative scale. These tests are relatively imprecise and reflect a range of protein concentrations(1):

1+ (30-99 mg/dl)	2+ (100-299 mg/dl)
3+ (300-999 mg/dl)	4+ (>1000 mg/dl)

Microscopic examination is carried out on the urine sediment prepared in a standard way (10 ml urine is centrifuged at 1500 rpm for 5 minutes, 9 ml of supernatant is pipetted off and the sediment is resuspended in remaining 1 ml). Five or more RBC per high power field indicate significant abnormality. Uncentrifuged urine can be examined in a counting chamber; 20 or more RBC/cu mm are considered abnormal. Red cell casts are seldom found in microscopic hematuria; their presence indicates a glomerular pathology. While heavy hematuria of either upper or lower tract origin will be accompanied by some proteinuria, persistent heavy proteinuria more than 2+ is virtually diagnostic of glomerular disease (*Table I*).

Red Cell Morphology (*Table I*)

Experienced observers can detect dysmorphic RBC in a fresh preparation of urine on light or phase contrast microscopy(2). Such cells are of various sizes and shapes, appear pitted and distorted with irregular outlines and have non-homogeneous cytoplasm. The presence of more than 20-40% of such cells indicates a glomerular

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TABLE I—*Glomerular versus Extraglomerular Hematuria*

Urinary finding	Glomerular	Extraglomerular
Red cell casts	May be present	Absent
Red cell morphology	Dysmorphic	Eumorphic
Proteinuria (2+ or more)	May be present	Absent
Clots	Absent	May be present
Color	Red or brown	May be red

site of origin of RBC. In addition, the presence of more than 5% acanthocytes (ring forms with vesicle shaped protrusions), in urine, closely correlates with glomerular disease(3). Eumorphic RBC in urine resemble normal circulating RBC and are derived from renal pelvis or lower urinary tract.

Gross Hematuria

The presence of hematuria must be confirmed by microscopic demonstration of RBC. Hemoglobinuria (usually caused by a severe intravascular hemolysis), myoglobinuria (occurring after extensive muscle trauma or occasionally strenuous exercise), porphyria, ingestion of sugar-beet, drugs including rifampicin and presence of pigments in food articles, may also result in passage of red colored urine.

Gross hematuria associated with other symptoms is usually caused by acute glomerulonephritis (GN) (edema, hypertension, oliguria), urolithiasis (colicky pain, flank pain, dysuria), and acute urinary tract infection (fever, flank pain, dysuria, suprapubic pain). Asymptomatic gross hematuria may occur in acute or chronic GN, IgA nephropathy, hydronephrosis (often precipitated by minor trauma), hypercalciuria, Wilms' tumor, coagulation disorders and rarely arterio-venous malformations in the kidney or urinary tract. Hematuria occurring at the beginning of micturition suggests a lesion in the urethra, and that towards the end (terminal hematuria) a pathology in the bladder.

Appropriate laboratory investigations are likely to establish a diagnosis in more than half the cases presenting with gross hematuria(1,2).

Asymptomatic Microscopic Hematuria

Screening studies of healthy school children reveal a varying prevalence of microscopic hematuria, depending upon the criteria used and whether multiple specimens were examined(4). With more frequent use of the convenient dipstick method, a trace of 1+ of blood is being detected with a greater frequency on incidental urine tests(4). Most cases are due to primary glomerular disorders, however surgically remediable causes are occasionally diagnosed, and it is necessary that every child be appropriately investigated(5). Important causes of asymptomatic microscopic hematuria are listed in *Table II*.

1. *Proliferative GN*

A large proportion of cases of acute post-streptococcal GN, especially during an epidemic, have no symptoms and are detected on urine examination. Microscopic hematuria of varying degree may be

TABLE II—*Causes of Asymptomatic Hematuria*

A. *Glomerular*
Acute glomerulonephritis
Chronic glomerulonephritis (Focal Glomerulosclerosis; membranoproliferative GN)
Henoch Schonlein purpura, IgA nephropathy
Alport syndrome
Benign hematuria, familial or sporadic; thin membrane disease
B. *Non-glomerular*
Urinary tract infection
Idiopathic hypercalciuria
Urolithiasis
Urinary tract malformations
Sickle cell disease
Interstitial nephritis
Tumors (Willms' tumor, leukemia)

the only abnormality. Complete spontaneous recovery is the rule. The diagnosis can be confirmed by the finding of low levels of serum complement (C3) and raised ASO titres; both return to normal within 6-12 weeks of the onset of the renal disease.

Hematuria may occasionally be the first symptom in membranoproliferative GN; persistent heavy proteinuria and low C3 concentrations are usually associated. Hematuria is the commonest renal manifestation of Henoch-Schonlein purpura. While presence of the systemic features usually indicates the diagnosis, an occasional patient may present with asymptomatic hematuria after the initial illness has resolved.

2. *Idiopathic Hypercalciuria*

Idiopathic hypercalciuria has been shown to be a common cause of microscopic as well as gross hematuria(6). The incidence and natural history of idiopathic hypercalciuria in children is not known. Calcium containing microcalculi cause irritation of the renal tubular epithelium and bleeding. A family history of urolithiasis may be present. A urinary calcium excretion of over 4 mg/kg/24 h or 'spot' urinary calcium to creatinine ratio of more than 0.21 is abnormal. This disorder should be carefully diagnosed since management with a high fluid intake, low calcium diet and hydrochlorothiazide will reduce urinary calcium excretion, stop hematuria and prevent stone formation.

3. *IgA Nephropathy*

This disorder is distinguished by the diffuse deposition of IgA in the glomerular mesangium. Typically IgA nephropathy is associated with recurrent gross hematuria, but occasionally it is detected on investigation of microscopic hematuria(7). The course of the illness is protracted. A few children may develop focal segmental sclerosis, and are at a risk of chronic renal failure(8).

4. *Alport Syndrome (Hereditary Nephritis with Deafness)*

Microscopic hematuria may be the only abnormality for several years. A history of renal disease and sensorineural deafness in the family gives a clue to the diagnosis. However, such a history may not always be obtained, since female 'carriers' may have asymptomatic microscopic hematuria as the only clinical manifestation(9). It is, therefore, important to test the urine of all first degree relatives of children presenting with hematuria, before dismissing the disorder as non-familial(5).

5. *Benign Hematuria*

In a majority of healthy asymptomatic children with microscopic hematuria, no cause can be found. In a small group of such patients, siblings and other family members also have microscopic hematuria. Electron-microscopic examination of the glomeruli show abnormal thinning of the capillary basement membrane (thin-membrane disease)(5,10,11). The condition is probably benign; chronic renal failure of late onset has, however, been reported(10,11).

In many other children, microscopic hematuria spontaneously disappears over a period of a few years.

Management of Asymptomatic Microscopic Hematuria

A careful clinical evaluation should be done. A history of renal disease in the child (dysuria, abdominal pain, abnormal micturition pattern, polyuria, intake of nephrotoxic drugs, edema, hematuria, hypertension), and in the family should be obtained. Physical examination of the child should include assessment of growth and evidence of an acute or chronic renal disease such as edema, hypertension, unexplained anemia, bony abnormalities and growth retardation. Any suggestion of deafness, from the history or examination, requires an audiogram for confirmation.

If features suggesting the likelihood of a renal parenchymal disease (proteinuria, azotemia, hypertension) are present, evaluation of renal function and a renal biopsy would be required.

In case isolated microscopic hematuria is the sole abnormality the following investigations may be carried out:

(*i*) Estimation of the level of blood urea or creatinine.

(*ii*) Measurement of urinary calcium excretion (24 h urine collection or urine calcium/creatinine ratio on a random specimen).

(*iii*) Ultrasonographic examination of the kidney and urinary tract is gradually replacing "intravenous pyelography (IVP)". Considerable investigator experience is, however, necessary for the former, particularly in case of young children and infants. If facilities for ultrasonography are not available, an IVP should be performed with careful precautions (the child should be well hydrated and abdomen free of gas shadows). An invasive procedure such as cystoscopy is considered only if there are definite features suggesting a lesion in the bladder or the urethra.

If these investigations do not reveal abnormalities, further tests may not be required at this stage. The child must, however, be kept under follow-up for a prolonged period until hematuria disappears. Clinical examination (growth, blood pressure), urinalysis (degree of hematuria, proteinuria), should be done at 6 month intervals. In case hematuria persists beyond two years, or additional abnormalities suggesting a renal parenchymal disease appear, a renal biopsy may be considered.

Asymptomatic Proteinuria

Proteinuria (1+ to 2+) occuring transiently after heavy exercise, fever and dehydration is of no significance. In all such cases urinalyses should be repeated to ensure that proteinuria does not persist.

Accurate quantitative measurements of urinary protein are usually not necessary if careful semiquantitative tests are done on a concentrated (first morning) specimen. Protein excretion of 100 mg/m^2 to 1 g/m^2 in 24-h indicates mild to moderate proteinuria; more than that is considered "heavy" and if persistent may lead to the nephrotic syndrome. An alternative to the 24-h urine collection is the protein to creatinine ratio in a random specimen; this ratio correlates closely to the total protein excretion(12). An early morning urine protein to creatinine ratio of more than 20 mg : mmol, or albumin (mg) to creatinine (mg) ratio of more than 1 is significant(11,13). Important causes of persistent proteinuria are listed in *Table III.*

1. *Orthostatic Proteinuria*

Mild to moderate proteinuria (rarely more than 1 g/24 h), without associated hematuria, occurring during upright posture is a common cause of otherwise unexplained proteinuria(1). The condition should be excluded by testing the urine passed during recumbency and subsequently after usual activity. The child empties the bladder before going to bed. Urine voided at night, as well as the first morning specimen before he gets out of bed are tested for protein, and should not give more than a trace reaction (50-100 mg). Later specimens with the child up and about, show 2+ or 3+ proteinuria (200-800 mg)(1,14).

TABLE III—*Important Causes of Persistent Proteinuria*

1.	Orthostatic proteinuria (transient, fixed)
2.	Benign persistent proteinuria
3.	Chronic glomerular disease (focal segmental glomerulosclerosis, membranous nephropathy, proliferative glomerulonephritis)
4.	Hereditary nephritis (Alport syndrome, others)
5.	Reflux nephropathy
6.	Renal hypoplasia
7.	Renal tubular disorders, interstitial nephritis

The pathogenesis of orthostatic proteinuria is not clear(15). Abnormalities of renal hemodynamics during erect posture have been found. The condition is regarded as benign(1,16), although rarely chronic glomerular damage may occur after several years. Thus, whereas an overall good prognosis can be given and parents reassured, a long term follow-up with yearly evaluation is necessary.

A variant of orthostatic proteinuria, *benign persistent proteinuria* is characterized by moderate protein excretion throughout the 24-h cycle, physical examination and investigations are normal(1).

2. *Persistent GN*

Several forms of GN particularly focal segmental glomerulosclerosis, may be characterized by asymptomatic proteinuria for varying periods before other abnormalities appear. Microscopic hematuria is usually associated. A renal biopsy is necessary for diagnosis.

3. *Reflux Nephropathy*

Chronic renal damage from vesicoureteric reflux and urinary tract infection may be evidenced by proteinuria. A history suggestive of urinary infection may not be always present. The reflux can be demonstrated by contrast or radionuclide cystourethrography; the IVP may show calyectasis and cortical scars.

4. *Renal Hypoplasia*

Reduction of renal mass may eventually lead to damage of the remaining nephrons (renoprival nephropathy), which is manifested by proteinuria and later other features of chronic renal insufficiency.

5. *Renal Tubular Disorders*

Defective tubular absorption (*e.g.*, Fanconi syndrome) or other forms of tubular injury may lead to increased urinary protein excretion. Such proteinuria is usually mild and predominantly consists of low molecular weight alpha and beta globulins. Albumin constitutes most of the protein in "glomerular" proteinuria.

Indications of Kidney Biopsy

Renal biopsy should be carried out if both proteinuria and hematuria are present, there is history of renal disease in the family or evidence of chronic renal disease in the patient, proteinuria is heavy or persistent, and if during the period of follow-up renal functional impairment or hypertension develop. The procedure is necessary to diagnose IgA nephropathy, Alport syndrome and other persistent GN. It is essential that the biopsy examination be carried out at a centre where expert morphologic evaluation with light microscopy, electron microscopy and immunofluorescence examination is available. A renal biopsy examined in this manner will provide diagnostic and to some extent prognostic information, and help in planning future therapy.

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Emergency Tips

Fever Without Focus

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Fever is one of the commonest symptom in a sick child. It accounts for more than 50% of visits to our Pediatric emergency service. Many febrile children have a variety of characteristic signs and symptoms indicative of a specific infectious or noninfectious disease. Others especially those under 36 months of age and with underlying malnutrition may have more subtle and nonspecific signs of disease. Such patients account for 4-5% of the total visits to our Emergency service. The major concern in such febrile children with no evident focus is rapid and early detection, and treatment of serious bacterial infections (SBI) and bacteremia which can otherwise lead to serious and life threatening consequences. Life-threatening non-infectious illnesses especially heat-stroke, and certain poisonings which may also present predominantly as fever and nonspecific signs and symptoms are uncommon compared to bacterial infections.

What are the specific variables that may help in selecting those febrile children below 3 years of age who are 'at high risk' of 'low risk' of serious bacterial infection?

Is the Temperature Grade Helpful?

Pantell *et al.*(1) found that in infants <3 months of age fever >38.3°C was associated with a 21.5 times the risk of serious underlying infection than infants >3 months with a similar temperature. Temperatures ≥39°C appear to be linked with a higher risk of bacteremia and bacterial infections. In an analysis of the published data McLellan and Giebank found that the probability of a temperature >39°C in children with proved bacteremia was as high as >90% and low grade fever was an excellent discriminator of absence of bacteremia(2). The evidence that temperature >41°C (hyperpyrexia) is associated with a higher risk of serious bacterial infection than a temperature between 39-41°C is poor. Alpert *et al.*(3) in a restrospective case-control study compared three groups of 76 children each, with temperatures between 39.1–40°C, 40.1–41°C and >41.1°C. Bacteremia was detected in seven children; only one of them was hyperpyrexic, while four had temperature 40.1°–41°C. The only child in the study who had meningitis had a temperature of 39.1–40°C. The data suggest that in previously healthy children, 2-36 months of age, a temperature between 39-41°C is associated with as much risk of SBI as any hyperpyrexia and should receive as much attention. Temperature <39°C of

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