Haematuria and proteinuria in childhood

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Abstract

Haematuria and proteinuria are common findings on urinalysis in childhood. They typically occur in three situations; firstly in patients with specific symptoms e.g. macroscopic haematuria or nephrotic syndrome, secondly in patients who have non-specific symptoms (usually when looking to exclude urinary tract infection) and thirdly in asymptomatic children. For the majority of children in the latter two groups the finding is temporary and not associated with long term renal disease. If the finding is persistent or patients have specific clinical features then renal abnormalities are more likely and appropriate investigation is required. This review provides a rationale for an approach that allows reassurance to be given to children and their families in whom the finding is transient and benign, whilst identifying those in whom renal abnormalities are present and treatment required. It describes algorithms for macroscopic haematuria (MaH), asymptomatic microscopic haematuria (MiH) and proteinuria.

Keywords childhood; chronic kidney disease; glomerulonephritis; haematuria; nephrotic syndrome; proteinuria

Definitions

Whilst there is no consensus regarding a definition of microscopic haematuria (MiH), a reasonable approach is to assume that more than five red blood cells (RBC) per millilitre of uncentrifuged urine, or 5–10 RBC per high-powered field for resuspended urine sediment, constitutes MiH. Automated urine microscopy devices are more sensitive and do not correlate with these levels but can be used to confirm haematuria if detected on urine dipstick.

It is important to appreciate how the urine dipstick detects haematuria and proteinuria and its limitations. Haemoglobin catalyses an oxidation reaction between hydrogen peroxide and tetramethylbenzidine impregnated on the dipstick, affecting a colour change from yellow to green. Other oxidising agents (e.g. free haemoglobin and myoglobin) can cause colour change in the absence of red blood cells, providing false positive results.

Macroscopic haematuria (MaH) refers to visible blood in the urine, appearing red or brownish in colour. However, all that is red or brown is not always blood. Box 1 provides a list of causes of red or brown urine without RBCs. In children who are unwell and those with MaH or persistent MiH, it is necessary to confirm a positive dipstick result with urine microscopy.

Screening for proteinuria is usually performed with urine dipstick, which measures albumin concentration by colourimetric reaction between albumin and tetrabromophenol blue. Although giving a guide to the presence or absence of proteinuria, the degree of proteinuria correlates poorly with laboratory quantification. False negative results occur in low molecular weight proteinuria (see 'Tubular Proteinuria' below) and false positive results may occur in very alkaline urine or within 24 hours of iodinated radiocontrast administration. Abnormal results should be confirmed with laboratory testing. Proteinuria in adult practice is frequently quantified with a 24 hour collection. This is impractical in children and a spot urine sample for protein:creatinine ratio in the early morning is a well validated method. Urine albumin:creatinine ratio is generally more expensive and has poor sensitivity for tubular proteinuria. An early morning urine sample should be collected to avoid elevated levels secondary to orthostatic proteinuria. Normal values are less than 15 mg/mmol, levels greater than this but less than 50 mg/mmol require repeat samples for confirmation. Levels greater than 50 mg/mmol are abnormal, greater than 100 mg/mmol significantly abnormal and greater than 300 mg/mmol nephrotic range proteinuria.

Incidence

The incidence of MaH in a general paediatric population is 0.13%. Persistent MiH occurs in 0.5%–2% of children, varying with definitions of 'persistent' and 'haematuria'. Proteinuria is found in up to 2.6% of children in population screening programs, reducing to less than 0.8% if repeat testing is performed. Though the American Academy of Pediatrics advises screening on school entry, the role of population childhood screening remains controversial.

Aetiology

The differential diagnosis of paediatric haematuria ranges from benign transient or familial traits to insidious, chronic or acute medical conditions. A comprehensive list of causes of paediatric haematuria is presented in Box 2.

Proteinuria is also associated with benign conditions and can be seen in fever, exercise or orthostatic proteinuria. If associated with haematuria or if significantly raised it is more likely to be associated with renal disease. A list of causes of proteinuria in the paediatric population is presented in Box 3.

Non-haematuria aetiologies of red or brown urine

- Filtered free haemoglobin (dipstick positive)
- Filtered myoglobin (dipstick positive)
- Drugs (e.g. rifampicin, doxorubicin, nitrofurantoin, metronidazole)
- Food pigments (e.g. betalaine in beetroot)
- Inborn errors of metabolism (e.g. porphyrinuria, tyrosinaemia, methaemoglobin)
- Neonatal urate crystals (normal, transient phenomenon giving 'brick-dust' appearance to the urine of a newborn)

Box 1

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Causes of Haematuria in Children

Glomerular
- Post-infectious glomerulonephritis (PIGN)
- IgA Nephropathy (Berger's disease)
- Benign familial haematuria
- Other glomerulonephritides (HSP nephritis, SLE nephritis, etc)
- Exercise

Tubulointerstitial
- Pyelonephritis
- Renal cystic dysplasia
- Sickle cell disease/trait
- Coagulopathy
- Tuberculosis

Lower urinary tract
- Urolithiasis
- Hypercalciuria without urolithiasis
- Haemorrhagic cystitis (e.g. adenovirus, cyclophosphamide)
- Idiopathic bulbar urethritis
- Tumours (e.g. Wilm's tumour, angiomyolipomata)
- Loin pain haematuria
- Schistosomia haematobium infection

Vascular
- Renal vein thrombosis
- Nutcracker syndrome

Box 2

Causes of proteinuria

Intermittent
- Fever
- Exercise
- Orthostatic (postural)

Primary glomerular
- Minimal change disease
- Focal segmental glomerular sclerosis
- Congenital nephrotic syndrome
- Membranoproliferative Glomerulonephritis

Secondary glomerular — frequently associated with haematuria
- Post-infectious glomerulonephritis (PIGN)
- IgA nephropathy
- HSP nephritis
- SLE nephritis
- Alport's syndrome
- Haemolytic uraemic syndrome

Other
- Diabetes mellitus
- Hypertension
- Reflux nephropathy

Tubulointerstitial
- Proximal renal tubular acidosis
- Cystinosis
- Lowe's syndrome
- Pyelonephritis
- Interstitial nephritis
- Acute tubular necrosis
- Drugs

Box 3

Clinical evaluation

Clinical evaluation varies depending on the specific presentation. We have classified patients into the following groups:

1. Macroscopic haematuria or symptomatic microscopic haematuria
2. Asymptomatic microscopic haematuria
3. Isolated proteinuria in children with symptoms or known renal disease
4. Asymptomatic isolated proteinuria

In all children with haematuria or proteinuria a clinical evaluation should include blood pressure measurement compared to a reference of normal values for the child's gender and height. Confirmation should be obtained by microscopy, urine protein:creatinine ratio and in the case of MaH or if specific clinical features by urine culture. Further evaluation is dependent on whether the child is unwell and any specific clinical features.

Features suggestive of renal disease requiring urgent investigation are fluid overload, oedema, ascites, oligoanuria, hypertension or haematuria accompanied by significant proteinuria. Systemic symptoms such as joint pain or swelling, a vasculitic rash, the presence of previous episodes and significant past medical history such as recent upper respiratory tract infection, growth impairment or hearing abnormalities also require further investigation. The presence of a family history of haematuria, renal disease or hearing impairment suggests a familial cause.

1) Macroscopic haematuria or symptomatic microscopic haematuria

The majority of cases of MaH are urinary tract infection (UTI), urinary tract trauma or periurethral/perineal irritation however the differential diagnosis is broad. It is useful to differentiate between glomerular and lower urinary tract (LUT) causes on clinical grounds to target investigations and guide initial management.

LUT bleeding is typically red or burgundy in appearance. The presence of blood clots passed per urethra strongly suggests LUT bleeding. Red urine isolated to the early stream suggests a urethral focus, whilst terminal stream haematuria suggests a bladder focus (e.g. cystitis, calculus, schistosomiasis). Pain is more suggestive of a LUT source although dull flank pain can present in glomerular diseases.

A brownish-red or 'cola-coloured' urine suggests glomerular bleeding. Signs suggestive of glomerulonephritis include hypertension, signs of fluid overload (including raised jugular venous pressure, peripheral and pulmonary oedema), and/or proteinuria (usually greater than 50 mg/mmol creatinine). Whilst their absence does not exclude glomerulonephritis, the presence of any of these signs should prompt urgent biochemical assessment of renal function. Dysmorphic red blood cells and cellular casts are also sensitive for glomerular bleeding on urine microscopy.