Personal Practice

Diagnostic Approach to a Child with Hematuria

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Children presenting with hematuria is a frightening situation for the child, parent, pediatrician and the pediatric nephrologist Actions include detailed history taking, physical examination, relevant investigations and reassurance If hematuria is non-life threatening and a cause is not ascertained, children can be kept under surveillance and reevaluated periodically or when hematuria recurs.

Definitions

Macroscopic Hematuria Child is brought with the symptom of hematuria The diagnosis is obvious and has to be differentiated from pseudohematuria wherein urine is colored red Confirmation by dipstick and sediment examination is necessary to differentiate between true hematuria, pigmenturia and interfering compounds in the urine due to ingestion of rifampicin, colored food and beet root.

Microscopic Hematuria The term indicates the presence of abnormal number of RBCs in the urine. What constitutes the abnormal number? There is no consensus about the number of RBCs necessary to define microscopic hematuria Passage of more than 1 million of RBCs in 24 hours is abnormal The presence of more than 5 RBCs per HPF is abnormal in a centrifuged specimen of urine The deposit is prepared from 10 ml of freshly voided urine, centrifuged at 2000-3000 revolutions per minute for 5 minutes and deposits resuspended in 1 ml of urine(1) However, in clinical practice it is normal to see 1 RBC per 2-3 HPF in a freshly voided uncentrifuged urine More than 3 cells per HPF in an uncentrifuged urine specimen is definitely abnormal and anything in between these two values should warrant repeat examination on two or three occasions on different days RBCs in more than one specimen of urine is an indication for further evaluation

Clinical Classification

Hematuria can be transient, persistent, symptomatic, asymptomatic or isolated

Transient hematuria Fever, infections, trauma and exercise are common causes and are usually microscopic and benign.

Persistent hematuria: Persistent presence of RBCs with or without other cellular deposits or recurrent macroscopic hematuria This usually indicates renal disease.

Symptomatic hematuria: Occurs in association with other symptoms such as hypertension, edema and urinary symptoms Always indicates underlying disease and needs detailed evaluation.

Asymptomatic hematuria: It can be macroscopic but it is usually microscopic and may be the sole abnormality with neither history nor physical examination providing

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indication of a systemic, renal or urological disorder. Long term follow-up is necessary to identify a benign or a slowly progressive disease process.

Isolated hematuria: This definition includes both gross and microscopic hematuria. Severe renal histologic abnormalities in children with persistent isolated hematuria is unusual(2). Persistent microhematuria interspersed with episodes of gross bleeding or with proteinuria signifies serious illness. These children need long term follow up as hematuria can disappear, or the child can develop additional renal or systemic abnormalities, or rarely isolated hematuria can persist.

Detection of Hematuria

Hematuria can be diagnosed by urine dipstick. This test is capable of detecting even five RBCs per cu mm, and is positive both in hemoglobinuria and myoglobinuria. It will be negative in discoloration of urine due to food and drugs. A positive dipstick test should be followed by microscopic examination of the urine to distinguish hematuria from myoglobinuria and hemoglobinuria. RBCs and RBC casts are absent in hemoglobinuria and myoglobinuria but dipstick for blood is positive. In hemoglobinuria the RBC lysis can lead to anemia; reticulocyte count is often increased. In hematuria though the loss of blood appears large, the children are not anemic unless the hematuria is due to a bleeding diathesis. A bedside approach is to centrifuge a fresh specimen of urine. In hemoglobinuria, the supernatant fluid will be clear pink with minimal or no deposits. In hematuria, the supernatant will be cloudy red or dark brown with RBC deposit.

Causes of Hematuria

Hematuria in children can be due to systemic and renal causes (*Table I).* Renal causes include glomerular and non-glomerular conditions. In systemic diseases the hematuria is due to bleeding from any part of the kidney and renal tract as a part

TABLE I-Causes *of Hematuria*

Systemic **disease**
Disseminated intravascular coagulation (DIVC)
Anticoagulant therapy
Snake bite envenomation
Hemorrhagic diseases
Thrombocytopenia
Glomerular disorders
Acute glomerulonephritis
Chronic glomerulonephritis
IgA nephropathy Systemic
vasculitis Hereditary nephritis
Benign familial hematuria
Renal vein thrombosis Acute
cortical necrosis
Nonglomerular disorders
Hypercalciuria
Genitourinary anomalies with infection
Viral hemorrhagic cystitis
Tumors
Polycystic kidney disease
Renal stone disease
Trauma
Foreign body
Sickle cell hemoglobinopathy
Urinary tract infection
Conditions mimicking hematuria (psuedohe-maturia)
Foods containing beetroot
Drugs- furazolidone, pyridium, rifampicin
Pigmenturia - hemolgobinuria, myoglobinuria, bilirubinuria

of generalized bleeding disorder. Common causes are DIVC, hemorrhagic disease and thrombocytopenia. In glomerular disorders common causes include acute glomerulonephritis, chronic glomerulone-phritis, IgA nephropathy and systemic vasculitis. Common causes of nonglomeru-lar hematuria are hypercalciuria, genitourinary anomalies with infection, renal stone disease and tumors. Even UTI alone can cause hematuria. There are conditions mimicking hematuria. Urine can get discolored following ingestion of foods containing beet root and drug intake like furazolidone. Pigmenturia can also mimick hematuria as in bilirubinuria.

In our clinical setting, DIVC and bleeding diathesis are the common systemic causes. Among the glomerular diseases, postinfective glomerulonephritis is the commonest followed by chronic glomerulonephritis like membranoproliferative and diffuse mesangioproliferative glomerulonephritis. Among nonglomerular disorders, urinary tract infection, acute cystitis due to adenovirus, hypercalciuric conditions, renal stone disease and lastly tumors form the frequent causes.

Mechanism of Hematuria

The morphology of RBC in urine in patients with glomerular disorders is usually abnormal. The mechanism of dysmorphism in glomerular disorders is due to the passage of RBCs through gaps in the damaged glomerular basement membrane(3). During this passage the morphology of the RBCs is modified by its intrinsic deformability, intraglomerular capillary pressure, size of the gaps, thickness of the glomerular basement membrane, variation in urine pH and osmotic pressure, and the effects of tubular enzymes. It has also been shown that lysis of few RBCs in the hypotonic distal tubular fluids, releases substances which can produce dysmorphism in other RBCs. In non-glomerular disorders direct injury to the tubulointerstitium by infections, stones and ischemic necrosis of papillae can produce hematuria. Tubular injury due to crystalluria, microcalculi and vascular ischemia due to disorders of micro-circulation are other mechanisms.

Types of Hematuria

Glomerular Hematuria

Presence of RBC casts indicate glomerular hematuria(4,5). Red cell casts are not usually seen in children with microscopic hematuria but if present indicate glomerular etiology(4). Persistent and heavy proteinuria of 2+ or more is usually indicative of glomerular hematuria. In nonglomerular hematuria there is usually mild proteinuria.

Studying the morphology of RBCs, in urine sediment, by phase contrast microscopy is more sensitive than Wright's stain or light microscopy(6). More than 15% dysmorphic RBCs were noted in urinary sediment of glomerular hematuria. Detecting acanthocytes by phase contrast microscopy also aids in the diagnosis of glomerular hematuria. Acanthocytes are identified by their unique ring form with vesicle shaped protrusions. When acanathocytes represent atleast 5% of total RBCs, an underlying glomerular disease can be diagnosed with a sensitivity of 52-99% and a specificity of 98-100%(3). Acanthocytes cannot be found in healthy subjects and in persons with exercise induced hematuria.

The other way of documenting glomerular hematuria is by studying G-l cells. Fresh urine is collected and observed by differential interference microscopy. The G-l cells are RBCs which have a distinctive dough nut like shape with blebs and is considered highly specific for glomerular

hematuria; more than 5% of such cells is significant(7).

Nonglomerular Hematuria

Asymptomatic hematuria due to hypercalciuria, in the absence of urolithiasis, can occur. Microcalculi irritating the urinary epithelium can produce hematuria. The condition presents with normocalcemic hypercalciuria and hematuria. Non-calculi disorders presenting as hematuria are also seen with hyperuricosuria and acquired hypero-xaluria(8,9). Hemangioma of the bladder(10) and rarely posterior urethral valves(11) can present in newborn period with hematuria. Congenital urethral polyps can also present as hematuria(12).

Exercise Related Hematuria

Some children following exercise can present with microscopic or macroscopic hematuria. Essentially they show glomerular origin of RBCs and few even show RBC casts(l). If urine analysis is normal otherwise and hematuria is documented only following exercise, further workup is usually not needed and these children are kept under surveillance(l).

Benign Familial Hematuria

Children with benign familial hematuria have first degree family members with hematuria but without history of chronic renal failure or sensorineural deafness(l). The hematuria is microscopic initially, later can be gross; proteinuria is mild or absent. Hypertension and renal failure are absent. Autosomal dominant inheritance, manifesting by 5 years of age and a non-progressive course are important features. Electron microscopy shows thin glomerular basement membrane(l).

Sickle Cell Disease

This form is seen chiefly in males. Hematuria may be microscopic or macroscopic, the left kidney is more commonly involved(l). There is RBC sickling and microvascular thrombosis due to medullary hypertonicity, low oxygen tension and acidosis, followed by rupture of *vasa recta* into the collecting system(1).

Evaluation

History

Family history of renal disease should be asked for and urinalysis performed in relatives. Presence of isolated, asymptomatic and nonprogressive hematuria in older relative often means a good prognosis and suggests benign familial hematuria. Heavy proteinuria, renal insufficiency, visual defects and deafness, at a younger age are suggestive of hereditary nephritis. An- other condition which may be familial is idiopathic hypercalciuria, where a history of urolithiasis in a relative is often present. The presence of synpharyngitic recurrent painless hematuria may denote presence of IgA nephropathy.

Clinical Examination

Presence of preceding impetigo or pharyngeal infection suggests poststreptococcal glomerulonephritis. Ecchymosis, purpura, petechiae, organomegaly, abdominal pain and joint pains suggest systemic vasculitis. Hearing loss, visual defects, keratoconus and lenticonus indicate hereditary nephritis. Distended bladder, palpable kidney, obstructive urinary symptoms and incontinence indicate congenital renal and urinary tract anomalies. Hypertension denotes renal parenchymal disease. Anemia is common in chronic glomerulonephritis, HUS and vasculitis.

Diagnosis

Once hematuria is confirmed it should be differentiated as systemic or renal. If

renal, is it glomerular or non glomerular? It is easy to identify systemic causes since hematuria is part of the systemic disease and there may be evidence of bleeding from other sites. Once systemic disease is ruled out the diagnosis is narrowed down to glomerular or nonglomerular hematuria. Glomerular bleeding is usually reddish brown in color with red cell casts, dysmorphic RBCs and proteinuria more than 2+. Glomerular causes can be associated with oligoanuria, edema and hypertension. The coffee ground or tea colored urine persists from beginning to end of micturition and is present throughout the day. Dysmorphic RBCs more than 15% under phase contrast microscopy suggests glomerular origin. In children with minimal hematuria as in acute glomerulonephritis the urine is usually clear. But on standing the hemoglobin from lysed cells undergo acid degradation and discolor urine to dark brown. The centrifuged urine will show smoky brown supernatant with reddish cellular sediment (red button appearance). The glomerular origin is confirmed on finding RBCs and hemoglobin casts. Presence of clots in the urine is not usual in glomerular disease.

It has also been found that Coulter counter can help to differentiate glomerular from non glomerular hematuria(3). At Coulter counter two clear cut volumes curves can be obtained according to the origin of RBCs. In glomerular bleeding mean corpuscular volume of urine RBC is about 50 cu fim whereas in nonglomerular disease it is about 100 cu |J.m. The presence of more than 5% of G-l cells in the freshly voided morning urine is also an indication of glomerular hematuria Hematuria of nonglomerular cause is macroscopic, bright red, intermittent and irregular. Hematuria might begin with micturition or be at the end. Renal colic, dysuria, stranguria and passage of blood clots, RBC clumps or stones with eumorphic RBCs more than 85% suggest nonglomerular cause.

Laboratory Evaluation

Collection of Urine

First urine passed in the morning and not the overnight urine in the bladder is to be examined. It should be a mid-stream specimen collected without catheterization. The RBCs are better preserved in fresh concentrated and acidic urine. Hence urine should be examined as soon as it is passed. Hematuria can be transient and examination should be repeated two or three times at intervals of few days.

Decision of Investigation

What investigation to do for the type of disease defined needs a practical approach and a protocol is given as a flow chart *(Fig.* 1)(13).

In the majority of cases the cause of hematuria can be identified without resorting to much investigations. Investigations are necessary to confirm the diagnosis and source of hematuria. Laboratory studies involve estimation of blood levels of urea and creatinine, blood counts and urine culture. The presence of significant proteinuria and elevated blood urea and creatinine indicate a glomerular disease. The presence of severe anemia suggests hemoglobinuria. Thrombocytopenia and coagulation abnormalities indicate a bleeding disorder. Increased urinary calcium, uric acid and oxalate indicates a nonglomerular cause.

Immunological evaluation includes estimation of serum complement, ASO titer, C-reactive protein, anti-nuclear antibodies and antineutrophil cytoplasmic antibody. Ultrasonogram is helpful in identifying urinary tract and renal anomalies, cystic diseases of kidney and calculi. IVP and

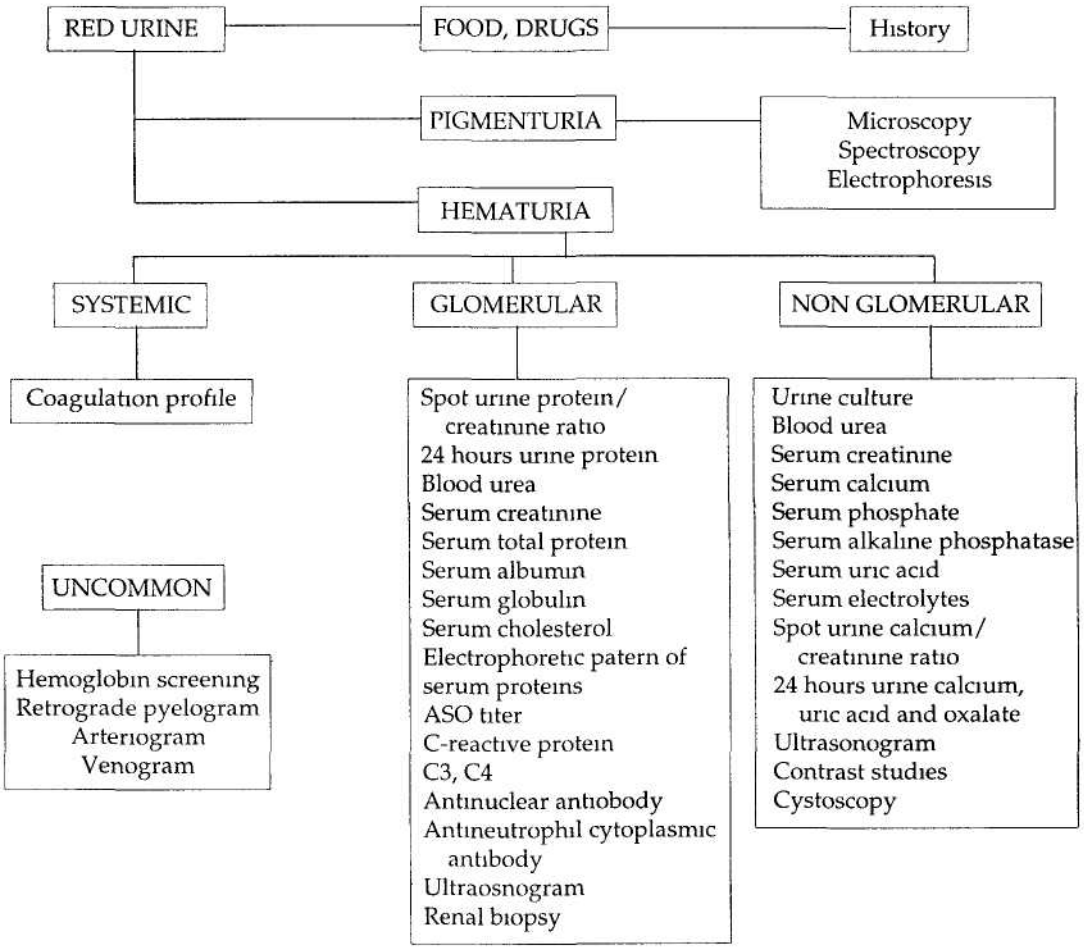

Fig 1 Flow chart for evaluation of hematuria.

voiding cystourethrography have value in nonglomerular hematuria. Cystoscopy may confirm a diagnosis in nonglomerular hematuria. Retrograde pyelography is useful when hematuria is suspected to be from one kidney. An audiogram should be performed in case of deafness in the family. Renal biopsy is indicated in glomerular disease with family history of progressive glomerulonephritis, recurrent glomerular hematuria, or when suspected to have systemic vasculitis. It should be accepted that in a small number of children the cause of hematuria will not be found and the they need surveillance. A step by step approach for the diagnosis of hematuria is given in *Fig.* 2(1,14).

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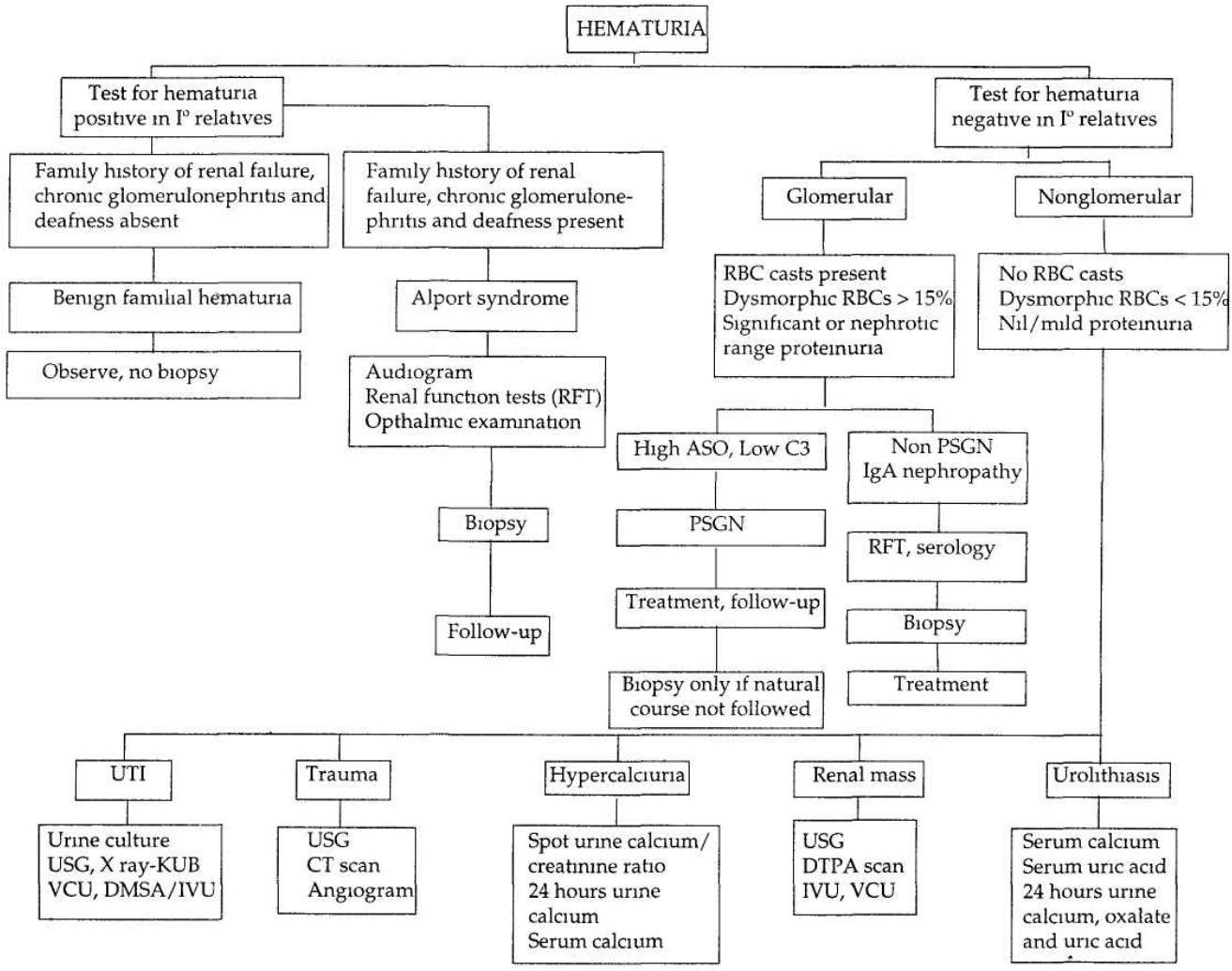

Fig 2 Step by step approach to hematuria

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