Evaluation of a Child with Hematuria

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Objectives

- What are the common clinical presentations?
- How to differentiate glomerular from non-glomerular hematuria?
- What are the common causes of hematuria?
- Overview of some of the common causes.
- Which patients are likely to have serious underlying disease requiring extensive workup?

Prevalence

One of the common reasons for nephrology consultation

Persistent hematuria is seen in 1 to 2% of children.


Usual Clinical Presentations

- Hematuria (microscopic) picked up during routine physical examination
- Episode of gross hematuria (first or recurrent)
- Hematuria with associated features of glomerulonephritis

Reagent Test-Strips

- Detects intact erythrocytes, as well as free hemoglobin and myoglobin
- False positive results with oxidizing contaminants such as hypochlorites, and Betadine®
- False negative results in the presence of high levels of ascorbic acid

Features Suggestive of Glomerulonephritis

- hematuria (cola colored)
- proteinuria (usually moderate)
- oliguria
- edema
- hypertension
- azotemia (↑ BUN, creatinine)
Isomorphic Dysmorphic RBC cast
Characteristic of glomerulonephritis

Hematuria:
Glomerular vs. non-glomerular

Causes of Hematuria

- Glomerular diseases:
  - Post infectious
  - Lupus nephritis
  - MPGN
  - chronic infections
  - IgA nephropathy
  - HSP nephritis
  - Thin basement membrane nephropathy
  - Alport syndrome
  - HUS
  - RPGN

- Hypermelioria / nephrolithiasis

- Pyelonephritis / cystitis

- Hemorrhagic cystitis

- Trauma

Anatomical:
- Cystic kidney disease
- UPJ obstruction
- Tumor
- AV malformation

Hematologic:
- smile cell
- RV thrombosis
- coagulopathies

Exercise

Rare & miscellaneous causes:
- Goodpasture syndrome
- Wegner’s
- Polyarteritis
- Nut-cracker syndrome
- Loin pain hematuria syndrome

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### Case Example

8 year old boy presents with history of dark cola colored urine, oliguria, and facial puffiness. He had throat infection 2 weeks ago. BP 130/90 mmHg, periorbital puffiness, systemic examination normal.

Urinalysis: Large blood, 3+ protein, TNTC RBC (dysmorphic) with RBC casts.

Labs: Sodium 141, potassium 5.1, chloride 107, CO₂ 25, BUN 25, creatinine 1.0, albumin 3.9, C₁₇ 16 (60 – 200), C₄ 20 (10 – 50), ASO 557 (< 200).
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Repeat Labs (8 weeks later): C₃ 96, C₄ 30.

Post Strep Glomerulonephritis

- Prototype of glomerulonephritis.
- Most common type of GN in children.
- Immune complex mediated GN.
- Common association with Gr. A β-hemolytic streptococcus (nephritogenic strains; serotype 12).
- Clinical attack rate 10 – 12%.
- Usually 7 – 14 days after infectious episode.
- Wide clinical spectrum (subclinical disease is 4 times more common than clinical disease).
- Depressed serum complement (usually only C₃); and evidence of recent strep infection (ASO, anti DNase B; or streptozyme test).

Post Strep Glomerulonephritis (Cont.)

- Treatment is symptomatic and recovery is spontaneous and usually complete.
- Antibiotics for Strep. eradication.
- Recovery usually starts in couple of weeks.
- Resolution of gross hematuria by 2 – 3 weeks.
- Complement levels normal by 8 weeks.
- Proteinuria resolves by 3 – 6 months.
- Microscopic hematuria can persist up to 1 year.

Post Strep Glomerulonephritis (Histopathology)

Indications for kidney biopsy:

- Normal complement levels at the onset
- Failure of normalization of complement levels by 8 – 12 weeks
- Nephrotic range proteinuria
- Severe ARF

Case Example

"17 yr AA girl, presents with history of progressive anasarca of 10 days duration with decreased and dark colored urine. Positive history of joint pains. BP 140/90 mmHg, anasarca, butterfly rash over face."
**Case Example**

“17 yr AA girl, presents with history of progressive anasarca of 10 days duration with decreased and dark colored urine. Positive history of joint pains. BP 140/90 mmHg, anasarca, butterfly rash over face.”

Urinalysis: Large blood, 4+ protein, TNTC RBC (dysmorphic) with RBC casts.

Labs: Sodium 140, potassium 4.6, chloride 115, CO₂ 19, BUN 41, creatinine 1.9, albumin 1.6, C₃ 15 (80 – 200), C₄ 6 (10 – 50), positive ANA.

**Lupus Nephritis**

“Glomerulonephritis is one of the most serious manifestations of SLE and is an important predictor of morbidity & mortality”

“Clinical renal involvement is noted in 40 – 80% of patients with SLE and is more common in children than adults”

**Pathophysiology**

Auto-antibodies

Immune complex

Deposition in Kidney

Activation of complement cascade

Recruitment of inflammatory cells

Genetic background

Hormones

Environmental factors
**Pathophysiology**

- 
  - Genetic background
  - Hormones
  - Environmental factors

Renal involvement can vary from minimal urinary anomalies to rapidly progressive renal failure.

**Clinical Presentation**

- **Proteinuria** is the most frequent symptom.
- **Hematuria** is frequently associated with proteinuria and is rarely seen in isolation.
- Patients with severe nephritis are often hypertensive and have reduced renal function.

**Histologic Classification**

- Most common and severe form of lupus nephritis.
- Hematuria, proteinuria, hypertension, decreased renal function.
- High risk of progression to ESRD if adequate therapy is not undertaken.
Membranous glomerulonephritis (Class V)

- Thickening of glomerular capillary walls.
- Little or no cellular proliferation.
- Severe proteinuria (nephrotic syndrome).
- Poor therapeutic response but prognosis not as bad as type IV.

Poor Prognostic Indicators

- Ethnicity (African-American)
- Socioeconomic situation
- Age (children)
- Sex (male)
- Elevated creatinine at presentation
- Hypertension
- Persistently elevated anti-dsDNA, and low C<sub>3</sub> & C<sub>4</sub>
- Diffuse lupus nephritis (Class IV)

Case Example

- "10 year old Caucasian boy, history of recurrent gross hematuria associated with URI. Episode lasts couple of days. Normal physical examination.

Urinalysis: Large blood, 2+ protein, 50 RBC (dysmorphic) with RBC casts.

Labs: Sodium 140, potassium 4.6, chloride 105, CO<sub>2</sub> 23, BUN 26, creatinine 0.7, albumin 4.2, C<sub>3</sub> 120 (80 – 200), C<sub>4</sub> 18 (10 – 50), serum IgA 550 (70 – 455).

IgA Nephropathy (Berger’s Disease)

- First described in 1968.
- Most common primary GN in the world.
- Higher prevalence in Japan, France, Italy, Australia (18 – 40%) than US (2 – 10%)
- Affects males > females.
- Pathogenesis unclear, immune dysregulation, IgA deposition in the mesangium.
Recurrent episodes of gross hematuria associated with URI is regarded as the hallmark (40% of cases).

Persistent asymptomatic microscopic hematuria with or without proteinuria.

Nephrotic syndrome.

Acute renal failure.

No clinical presentation is pathognomonic.

Normal serum complements.

Serum IgA levels are elevated in 30 – 50% of adults and 8 – 16% of children

Definite diagnosis is made with kidney biopsy.

Was once considered a benign disease.

Current knowledge: 5% develop CRF in 5 years and 10% by 15 years

Prognostic Indicators:

Persistent hematuria

Proteinuria

Hypertension

Tubulointerstitial changes on biopsy

Systemic form of the IgA nephropathy

Peak incidence ~ 5 years

50% renal involvement

Overall prognosis good
Case Example

“15 year old Caucasian boy has persistent microscopic hematuria for > 5 years. Over the years his hematuria has increased with increasing proteinuria. He also has progressive deafness and now needs hearing aids. His maternal uncle died with renal failure.”

Urinalysis: Large blood, 2+ protein, TNTC RBC

Labs: Sodium 136, potassium 4.8, chloride 101, CO₂ 22, BUN 42, creatinine 2.5.
Serum complement levels are normal.

Alport Syndrome (cont.)

- Most common hereditary nephritis.
- Caused by mutations in α3, α4, or α5 chains of Type IV collagen.
- 80% have X-linked form of the disease mutations of α5 Type IV.
- 15% are autosomal recessive due to mutations in both alleles of α3 or α4 on chromosome #2.
- 5% have heterozygous mutations of α3 or α4 but exhibit a progressive nephropathy associated with the characteristic Alport GBM lesion. This has autosomal dominant inheritance.

- Males more severely affected than females
- Progressive disease. Rate of progression is function of the causative mutation
- Phase I: from birth to late childhood or early adolescence. Characterized by hematuria and attenuation of GBM
- Phase II: Overt proteinuria in addition to hematuria but normal GFR
- Phase III: Declining renal function, interstitial fibrosis, tubular atrophy
- Phase IV: ESRD

- Family history of deafness and renal failure in male members.
- Normal serum complements.
- Sensorineural deafness, 50% by age 25, 90% by age 40 years.
- Ocular abnormalities: lenticonus.
- Characteristic histopathological changes seen on EM.
- Immunohistochemistry: 80% of the males and 60% of females exhibit abnormal expression of α3, α4, and α5 chains in kidney and α5 chain in skin.
Alport Syndrome (Histopathology)

- Autosomal dominant condition.
- Commonest cause of isolated microscopic hematuria.
- Persistent microscopic hematuria with minimal or no proteinuria.
- Attenuation of GBM (thickness < 200 nm).
- Genetic relationship with Alport (heterozygous mutation of α3 or α4 chain of type IV collagen).
- Generally good renal prognosis.

Thin Basement Membrane Disease (Benign familial hematuria)

- One of the common cause of frequency-dysuria, abdominal pain and hematuria syndrome.
- 2 to 5% of children with hypercalciuria will develop renal stones.
- Family history of kidney stones is common.
- Direct correlation with sodium intake.
- Urine calcium excretion > 4 mg/kg/day.
- Commonly diagnosed by checking Urine calcium to creatinine ratio.

Hypercalciuria

- Liberal fluid intake
- Low-salt, high-potassium diet
- Supplemental potassium citrate
- Thiazide diuretics

Thin Basement Membrane Disease

- Normal
- Alport Carrier

Hypercalciuria (Management)

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<tr>
<th>Race/Age Group</th>
<th>Median</th>
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<td></td>
<td>CS</td>
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<td>&lt; 7 months</td>
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<td>8 – 18 months</td>
<td>0.11</td>
<td>0.09</td>
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<tr>
<td>19 months – 6 years</td>
<td>0.10</td>
<td>0.06</td>
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<td>7 – 16 years</td>
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Patients needing detailed workup

- Significant persistent hematuria.
- Hematuria with significant proteinuria.
- Hematuria with reduced renal function.
- Family history of renal failure, deafness in early childhood.