Microscopic haematuria - who and when to refer

Stephen Marks
Consultant Paediatric Nephrologist

Great Ormond Street Hospital for Children and UCL Institute of Child Health, London, UK

Paediatric Nephrology for the General Paediatrician
Manchester, Friday 24 June 2016
Introduction

• Case presentations

• Does haematuria matter?

• Microscopic versus macroscopic haematuria

• Does management change with proteinuria?

• Evidence-based medicine

• Conclusions
Case presentations
Case 1

• 6 year old girl
  – developed viral URTI (sore throat and cough) 3w ago
  – both parents and her younger sister also had URTI
  – 48 hour history of vomiting, coca-cola urine
  – 24 hour history of periorbital oedema, oliguria
  – examination revealed
    • hypovolaemia, peripheral oedema, SBP = 130mmHg
  – investigations revealed
    • PCr of 150μmol/l, albumin 22g/l
    • proteinuria 3+, haematuria 3+, red cell casts
Case 2

- 3 year old girl
  - 6 month history of recurrent macroscopic haematuria
  - associated with precipitant of viral URTI
  - eating and drinking normally without vomiting
  - no family or past medical history
  - normal examination
  - investigations revealed
    - normal plasma creatinine and albumin
    - no proteinuria, haematuria 3+, no casts
    - no calculi on ultrasound
Case 3

• 12 year old boy
  – admitted with 4 day history of severe left loin pain
  – 3 week history of afebrile, recurrent episodes of macroscopic haematuria
  – decreased oral intake
  – examination revealed
    • severe left loin tenderness
  – investigations revealed
    • normal plasma creatinine and albumin
    • trace proteinuria, haematuria 4+, no casts
Case 3

• 12 year old boy
  – admitted with 4 day history of severe left loin pain
  – 3 week history of afebrile, recurrent episodes of macroscopic haematuria
  – decreased oral intake
  – examination revealed
    • severe left loin tenderness
  – investigations revealed
    • normal plasma creatinine and albumin
    • trace proteinuria, haematuria 4+, no casts
    • 2mm left non-obstructing renal calculus on ultrasound
Does haematuria matter?
Should we investigate?

**Macroscopic haematuria**  **Microscopic haematuria**
Should we investigate?

**Macroscopic haematuria**

**Microscopic haematuria**

YES
Should we investigate?

- **Macroscopic haematuria**
  - YES

- **Microscopic haematuria**
  - NO
Epidemiology of haematuria

Macroscopic haematuria
- Clear diagnosis
- 0.2% prevalence
- Resolution varies

Microscopic haematuria
- Definition varies
- 0.5-1.6% prevalence
- 70% resolution by 6m
Does haematuria matter?

- Only if recurrent macroscopic haematuria
  - always investigate if proteinuria present
- Exclude non-glomerular cause
- Exclude familial disorder
- Consider future of child
  - eg. occupation, insurance
Renal biopsies for recurrent macro or intermittent microscopic haematuria

n = 322 children
Microscopic haematuria
Urinalysis

• Convenient so widespread use
  – Store in dry environment
  – Automated results with printout

• Blood detected by peroxidase-like action and detects small quantities
  – Negative result excludes haematuria

• Protein detected by tetrabromophenol
  – Albumin demonstrates better binding
Microscopic haematuria

• May be asymptomatic
  – eg. family screening so consider BP, creatinine, UA:UC, renal biopsy and observe +/- treat

• Child with symptoms and/or signs
  – eg. fever, lethargy, hypertension, oedema

• Child with urinary tract symptoms
  – eg. dysuria, urgency, frequency, enuresis

• Child with non-urinary tract symptoms
  – eg. rash, purpura, arthritis, jaundice, GI
Microscopic haematuria

• Fever, illness, trauma and extreme exertion may induce haematuria
• Where haematuria is related to a non-renal disease, it should disappear with resolution of primary disease
• If patient has microscopic haematuria
  – > demonstrate resolution
  – > discharge if resolves or is intermittent over 6m with normal family dipstick, renal US, urine Ca:Cr
  – > if associated with proteinuria or is persistent or is associated with complex disease or FHx then refer
# Microscopic haematuria without proteinuria

<table>
<thead>
<tr>
<th>Cause</th>
<th>Investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI</td>
<td>MSSU M/C/S</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>Urine Ca:Cr</td>
</tr>
<tr>
<td>Renal calculi</td>
<td>Renal US</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>Renal US</td>
</tr>
</tbody>
</table>
# Renal biopsy for microscopic haematuria

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Invasive procedure</td>
</tr>
<tr>
<td>Avoid later Ix</td>
<td>No treatment</td>
</tr>
<tr>
<td>Genetic counselling</td>
<td></td>
</tr>
<tr>
<td>Reassurance</td>
<td>- unless develops proteinuria</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
</tr>
</tbody>
</table>
Population studies

160,000 Japanese children annually

251 (0.2%) isolated microscopic haematuria

136 (54%) asymptomatic microscopic haematuria

115 (46%) specific cause of microscopic haematuria
Isolated microscopic haematuria (n = 251 children)

- Asymptomatic isolated: 136 (54%)
- Normal / menstruation: 89 (35%)
- UTI (pyelonephritis / VUR 4): 14 (6%)
- Hypercalciuria (stone 1): 5 (2%)
- HSP nephritis (PMHx): 3 (1.2%)
- Hydronephrosis: 2 (0.8%)
- PKD: 1 (0.4%)

Prognosis of asymptomatic isolated microscopic haematuria

- Patients followed up for 7.4 (6-13) years
  - Hypertension: 0 (0%)
  - Renal impairment: 0 (0%)
  - Proteinuria: 1 (0.8%)
Microscopic haematuria

Glomerular haematuria

Proteinuria

Persistent/heavy

Renal biopsy

Haematuria persists

Follow-up

Accepted

Reassure

Rejected

Continuous haematuria

Family +ve

Nil or slight

Serial testing of child and
1st degree relatives

Intermittent haematuria, family -ve
Dipstick-positive hematuria

Urine sediment microscopy

< 5 RBCs/HPF
- Myoglobin-myoglobinuria
- Hemoglobin-hemolysis

> 5 RBCs/HPF
- Family history
- Family screen

Microscopic-negative protein
- Investigation
  - Urine C&S
  - Urine Ca:Cr ratio
  - Renal US

Macrosopic-negative protein
- Investigation
  - Urine C&S
  - Urine Ca:Cr
  - Renal US
  - VCU
  - Angiography
  - Renal biopsy
  - Immunoglobulins
  - C3, C4, ANA, ANCA

Micro/macrosopic-positive protein
- Investigation
  - 24-h Urine protein
  - C3, C4, ANA, ANCA
  - Immunoglobulins
  - Consider renal biopsy

See section on GN
Macroscopic haematuria
Visual examination of urine

• Macroscopic haematuria
  – may contain very small amounts of blood
    • cf. MICROSCOPIC HAEMATURIA MAY CONTAIN SIGNIFICANT NUMBERS OF RBCs
  – bright red blood staining may contain clots and indicates heavy bleeding
    • eg. TRAUMA, COAGULOPATHY

• Cloudy urine
  – pyuria associated with UTI

• Gravel
  – associated with calcium, urate, cystine or struvite
Bloody urine - without blood

• Cause of red urine without haematuria
  – Foods
    • eg. BEETROOT AND FOOD COLOURINGS
  – Drugs
    • eg. RIFAMPICIN
  – Haemoglobinuria
  – Myoglobinuria
  – Inborn errors of metabolism
    • eg. PORPHYRIA
  – Urate crystals
  – Factitious haematuria / MSBP
Bloody urine - without blood

- **Cause of red urine without haematuria**
  - **Foods**
    - eg. BEETROOT AND FOOD COLOURINGS
  - **Drugs**
    - eg. RIFAMPICIN

ALWAYS CONFIRM PRESENCE OF RED BLOOD CELLS ON URINE MICROSCOPY

- eg. PORPHYRIA
- Urate crystals
- Factitious haematuria / MSBP
Macroscopic haematuria

- Timing of haematuria
  - Renal cause
    - if throughout micturition
  - Bladder cause
    - terminal haematuria
    - non-specific urethritis
  - Urethral cause
    - at start of micturition
Causes of macroscopic haematuria

- Proven UTI 26%
- Suspected UTI 23%
- Perineal irritation 11%
- Trauma 6%
- Acute Nephritis 4%
- Coagulopathy 3%
- Stones 2%
- Tumour 1%
- Other 23%

Causes of macroscopic haematuria

- Exercise-induced
- Loin pain-haematuria syndrome
- Haemorrhagic cystitis
- Hypercalciuria
- Hyperuricosuria
- Bladder tumours / malakoplakia
  - eg. rhabdomyosarcoma
## Macroscopic haematuria without proteinuria

<table>
<thead>
<tr>
<th>Cause</th>
<th>Investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI</td>
<td>MSSU M/C/S</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>Urine Ca:Cr</td>
</tr>
<tr>
<td>Renal calculi</td>
<td>Renal US</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>Renal US</td>
</tr>
<tr>
<td>Papillary necrosis</td>
<td>Renal US</td>
</tr>
<tr>
<td>RVT</td>
<td>Doppler US</td>
</tr>
<tr>
<td>Others (eg.)</td>
<td>Urethral/bladder abnormalities</td>
</tr>
<tr>
<td></td>
<td>AV malformation, GN, SLE, IgA</td>
</tr>
<tr>
<td></td>
<td>nephropathy, SCD, SBE</td>
</tr>
</tbody>
</table>
Management of macroscopic haematuria

1. Confirm presence of RBCs on microscopy
2. History and physical examination (inc. BP)
3. MSSU -> treat if UTI
4. If non-confirmatory, family history and urinalysis with further investigations
   • FBC, coagulation screen, ESR, CRP
   • U&E’s, tCO2, albumin, ASOT, C3, C4, Ig’s. ANA
   • Urine dipstick, culture, albumin, urate and calcium:creatinine
   • Renal tract ultrasound +/- abdominal x-ray
5. Refer to paediatric nephrology
   • if renal impairment, proteinuria, hypertension etc
Developing proteinuria...
Proteinuria

- **Clinical evaluation**
  - macroscopic haematuria (menstruation)
  - evidence of oedema and/or hypertension

- **Bedside testing**
  - concentrated sample
  - orthostatic proteinuria (Early Morning Urine sample)

- **Laboratory testing (including tubular vs glomerular)**
  - nephrotic-range proteinuria (spot versus 24-hour collection)
    - EMU ALBUMIN : CREATININE RATIO, SERUM ALBUMIN
    - renal function
      - PLASMA CREATININE AND ESTIMATED GFR
    - percutaneous renal biopsy
Micro or macroscopic haematuria with proteinuria

<table>
<thead>
<tr>
<th>Cause</th>
<th>Investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>FBC, U&amp;E’s</td>
</tr>
<tr>
<td></td>
<td>C3, C4, ASOT</td>
</tr>
<tr>
<td></td>
<td>ANA, dsDNA</td>
</tr>
<tr>
<td></td>
<td>ANCA, Ig’s</td>
</tr>
<tr>
<td></td>
<td>Renal biopsy</td>
</tr>
</tbody>
</table>
Normal values (mg/mmol) for urine albumin : creatinine ratios

<table>
<thead>
<tr>
<th>Age</th>
<th>UA:UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1 w</td>
<td>3.0 - 44</td>
</tr>
<tr>
<td>1 w - 6 m</td>
<td>1.7 - 12.2</td>
</tr>
<tr>
<td>6 m - 2 y</td>
<td>1.5 - 8.7</td>
</tr>
<tr>
<td>2 - 5 y</td>
<td>0.5 - 3.3</td>
</tr>
<tr>
<td>5 - 10 y</td>
<td>0.2 - 4.5</td>
</tr>
<tr>
<td>10 - 16 y</td>
<td>0.1 - 7.4</td>
</tr>
</tbody>
</table>
↑ Urine protein

Nephrotic range proteinuria and oedema

no

Repeat with first morning urine
UA : UC

normal

Discharge

abnormal

Orthostatic proteinuria?

yes

Annual follow-up

no

U&E, albumin, lipids

Consider referral if abnormal features:
- age > 10 years
- evidence of systemic disease
- hypertension
- macroscopic haematuria

yes

Rx prednisolone
2mg/kg/day (<60mg)
Red blood cell cast
Dipstick test for protein

Repeat × 2

Negative
- Transient proteinuria
  - Not significant
    - Reevaluate at 12 mo

Positive
- Persistent proteinuria
  - Orthostatic test
    - Orthostatic
      - Not significant
        - Reevaluate at 12 mo
    - Not orthostatic
      - Significant
        - Quantify in 24 h
Glomerular origin

Renal function
ANCA, C₃, C₄, ANA
Consider renal biopsy

Tubular origin

Tubular function
Glycosuria
Aminoacidemia
Phosphaturia
Renal tubular acidosis
Impaired urine concentration
Treatment of proteinuria

- Immunosuppression for active GN
- ACE inhibitors and ARB treat hypertension and proteinuria
  - efferent arteriolar dilatation reducing glomerular pressure
  - commence Rx enalapril 0.1mg/kg/d
  - side-effects
    - ↑K and ↑PCr
    - non-productive cough
    - teratogen
Summary

• Microscopic haematuria
  – if continuous and confirmed RBC’s, check family members and exclude proteinuria and hypertension
  – discuss with family options of follow-up or biopsy

• Macroscopic haematuria
  – if recurrent and confirmed RBC’s, check timing during urinary stream to help isolate cause
  – investigations to exclude common conditions such as UTI and renal calculi

• Proteinuria
  – always investigate if persistent or non-orthostatic
  – exclude nephrotic syndrome and glomerulonephritis
Any questions?