FRACP course 2015
Glomerulonephritis- Nephrotic syndrome, haematuria, proteinuria

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Case 1
- An 8 yr old boy admitted to hospital with a 3 day history of swelling on his face, 2 days of dark urine and lethargy.
- Previously well, no history of sore throat, no skin lesions
- PMH: chronic otitis media
- Examination:
  Normally grown
  BP 145/90, mild peri-orbital oedema, otherwise well, neurologically normal
  No extra renal signs

Case 1 - labs
- urine - blood 4+, protein 3+
- Na+ 132, K 5.0, Urea 19.0, creatinine 110umol/l, albumin 25g/l
- Streptococcal serology: Normal
- Complements C3: 0.5(0.8-1.8)
- Urine PCR 500mg/mmol (<22)

Case 1 - question
What is the most likely diagnosis?
- a) IgA nephropathy
- b) Membranous glomerulonephritis
- c) Alports nephropathy
- d) post infectious glomerulonephritis
- e) Lupus nephritis
Question 2

The most appropriate management in this patient is

a) 20% albumin infusion
b) a thiazide diuretic
c) Fluid restriction to 400ml/m2
d) Intravenous sodium nitroprusside
e) oral calcium channel blocking agent

Haematuria

- persistent red cells in urine over a repeated number of occasions
- few rbc's are normally excreted in urine, due to normal passage through GBM
- excretion rate increases with age and exercise
- 1-3 rbc/hpf or 8000/ml urine is normal

How to detect blood in urine

- False +ve reactions occur with delay in reading
- Detects 0.015-0.03mg free Hb per 100 ml urine (5-20rbc/ul)

Haematuria

- Confirm by microscopy in fresh centrifuged specimen
- Glomerular haematuria
  - Dysmorphic RBCs
  - Red Blood cell casts
  - Concomitant proteinuria
- Non-glomerular
  - Eumorphic RBCs
  - Urinary tract
    - Ureter, bladder, urethra
Haematuria Differential

- Glomerular
  - IgA, Alport, Thin BM
  - Post-Infectious GN
  - SLE
  - Membranous Nephropathy
  - RPGN (Goodpastures, Wegeners)
  - HSP, HUS

- Medications
  - Diuretics
  - Aspirin
  - Anticonvulsants
  - Aminoglycosides
  - Cyclophosphamide

- Infection
  - Bacterial/Viral
  - TB

- Other
  - Sickle cell disease
  - Coagulopathy
  - Nephrolithiasis
  - Hypercalciuria
  - Renal Vein Thrombosis
  - Trauma
  - Structural Abnormalities
    - PKD
    - Vascular anomaly
    - Tumors

Don’t Forget UTI

- Important cause of haematuria
- Bacterial vs. Viral (adenovirus cystitis)

Haematuria - Initial assessment

- History
  - Frequency, dysuria, bed wetting
  - Loin pain, colic
  - Joint pain, rash, recent sore throat/infected eczema
  - Bleeding tendency
  - Deafness
  - Family history of kidney disease
  - Strenuous exercise
  - Tropical exposure

- Physical Exam
  - Oedema, volume overload, purpura, joint swelling
  - Renal mass, deafness, genital/anal bleed, BP

Haematuria - Initial investigations

- Urine
  - Urine microscopy: bacteria, wbc, casts, dysmorphic red cells, ova
  - Urine culture

- Urine chemistry
  - Protein excretion rate (uPCR)
  - Calcium, creatinine for ratio

- Blood
  - FBC, coagulation screen
  - Serum creatinine
  - C3 complement streptococcal titres (if haematuria<6mo)

- Imaging
  - Renal ultrasound – low yield
haematuria that needs urgent assessment?
• Hypertension
• Oedema
• Oliguria
• Heavy proteinuria
• Impaired renal function

Isolated haematuria (without significant proteinuria) is often benign

Acute nephritic syndrome (acute nephritis, acute glomerulonephritis)
• haematuria, hypertension, reduced GFR, mild - moderate proteinuria
• Usually acute onset with short preceding history of symptoms
• Common causes – PSGN, HSP, bacterial infections (strep pneumoniae, mycoplasma), viruses
• Severity varies from microscopic haematuria & normal renal function to syndrome of rapidly progressive loss of renal function (RPGN)
• Some may present as acute GN but typical do not resolve – SLE, MGPN, C3-GN

Post infectious glomerulonephritis
• History of preceding strep throat or skin infection
• acute onset gross hematuria
• Oedema, renal impairment
• Frequently hypertensive
• Depressed C3
• Haematuria may persist up to 2 years

Table 3 Clinical and laboratory features of children with APGN (n = 176) in New Zealand, September 2007-August 2009

| Clinical feature | n (%)
|------------------|-----
| Gross haematuria | 153 (87)
| Hypertension     | 126 (72)
| Oedema           | 109 (62)
| Oliguria         | 86/167 (51)

Elevated ASOT/AntiDNase B 138/175 (79)
Low C3 complement 161/173 (93)

Heavy proteinuria (U/Pc > 250/4+ dipstick) 58/133 (44)
Nephrotic syndrome 4/58 (7)
Paediatric glomerular diseases mimicking APSGN

<table>
<thead>
<tr>
<th>Preceding Infection</th>
<th>APSGN HSP Nephritis</th>
<th>Concurrent</th>
<th>IgA Nephritis</th>
<th>MPGN Type 1</th>
<th>SLE</th>
<th>ANCA Vasculitis</th>
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<tbody>
<tr>
<td>Yes</td>
<td>35%</td>
<td>concurrent</td>
<td>&lt;10%</td>
<td>20-50%</td>
<td>&lt;10%</td>
<td>Flu like prodrome</td>
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<tr>
<td>Gross Hematuria</td>
<td>30%</td>
<td>20%</td>
<td>50-80%</td>
<td>20-50%</td>
<td>&lt;10%</td>
<td>30%</td>
</tr>
<tr>
<td>Nephrotic</td>
<td>5%</td>
<td>5-10%</td>
<td>&lt;10%</td>
<td>30-50%</td>
<td>0-50%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>C3</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
<td>low</td>
<td>Normal</td>
</tr>
<tr>
<td>C4</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal Or low</td>
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<td>Normal</td>
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<tr>
<td>Diagnostic</td>
<td>ASOT</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>ANA dsDNA ANCA</td>
<td></td>
</tr>
<tr>
<td>Extrarenal Disease</td>
<td>Rare</td>
<td>Yes</td>
<td>Rare</td>
<td>Rare</td>
<td>common</td>
<td>common</td>
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</tbody>
</table>

Clinical and laboratory features

- Gross H:
- Hypertension
- Low C3
- Persistent proteinuria
- Intermittent proteinuria
- Microhaematuria

Time line to resolution of APSGN

Question

In post streptococcal glomerulonephritis, which of the following is correct

a) Chronic kidney disease occurs in up to 15% of affected patients
b) Rapidly progressive or crescentic glomerulonephritis is a recognised presentation
c) Hypertension is due excessive renin secretion
d) Serum complement C3 levels positively correlates with illness severity
e) Micro-haematuria usually resolves within 6 months of onset

Case History

9 year old Samoan boy

- Sore throat 2/52 prior to admission, treated with Amoxycillin
- No strep isolated from throat swab
- 5/7 progressive purpuric rash over lower limbs
- No joint swelling, no abdominal pain
- PHx unremarkable
Exam

- Systemically well
- BP 159/103 — increased to 187/122 while in CED (asymptomatic)
- Puffy around eyes

Question 1

What is the most appropriate course of treatment
a) Prednisone
b) Frusemide
c) Azathioprine
d) Oral antihypertensive agent
e) Hydroxychloroquine

Question 2

Acute glomerulonephritis in Henoch Schönlein purpura is expected to be mild in most children. When would you become most concerned?

a) Nephrotic syndrome at presentation
b) Persistent microscopic haematuria at 6mo follow up
c) Gross haematuria lasting 1-2 days in week of illness
d) Microscopic haematuria at presentation
e) Urine protein creatinine ratio 50-60mg/mmol at 4 weeks (normal uPCR<22)

Clinical features (Eur J Ped 2010;169:643-50)

<table>
<thead>
<tr>
<th>Organ involvement</th>
<th>incidence</th>
<th>description</th>
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<tbody>
<tr>
<td>skin</td>
<td>100%</td>
<td>Essential, may resemble urticarial or maculopapular rash before becoming papular, symmetrical</td>
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<tr>
<td>Joints</td>
<td>Up to 82%</td>
<td>Usually oligoarthritis, mainly lower limbs, self limiting</td>
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<tr>
<td>GI</td>
<td>50-75%</td>
<td>Mild to severe debilitating pain, bleeding common, intussusception, pancreatitis, hydrops</td>
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<tr>
<td>kidneys</td>
<td>20-60%</td>
<td>Commonly microhaematuria, gross haematuria, isolated HTN, mixed nephritic/nephrotic</td>
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<tr>
<td>urogenital</td>
<td>Up to 27% boys</td>
<td>orchitis</td>
</tr>
<tr>
<td>CNS</td>
<td>2%</td>
<td>Seizures, vasculitis, ICH</td>
</tr>
<tr>
<td>Lungs</td>
<td>&lt;1%</td>
<td>Interstitial pneumonia from alveolar bleeding</td>
</tr>
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</table>
Purpura generally symmetrical, affecting lower limbs and buttocks in majority of cases, upper extremities involved less frequently; abdomen, chest and face are generally unaffected.

New crops of purpura may develop for several months after the disease onset, generally fades with time.

Case history

A 13 year old presents her local paediatric service because of unilateral facial swelling, puffiness over legs for about 1 month before referral to medical services.

She has lost about 3 kg in weight,

No previous history of note.

Examination- mild swelling over ankles, BP 110/74

Her hands show...
Question

Investigation shows serum albumin 21g/L, creatinine 74umol/L, uPCR 1100, strep serology normal.
What is the next most appropriate investigation?

a) C3,C4 complement levels
b) Antinuclear antibody screen
c) Hepatitis B serology
d) Urine protein electrophoresis
e) Anti hyuronidase antibodies

IgA Nephropathy

• Most common GN
• Gross haematuria with illness-synpharyngitic
• Recurrent, may have flank pains
• Persistent microscopic haematuria

Alports Syndrome

• X-linked 80%, also AD and AR forms
• Hearing Loss
• Renal Failure
• Mutation in COL4

Alports Syndrome

• Mutation in gene encoding Type IV collagen which makes up the framework of the basement membrane
• EM shows basket weave appearance
• Anterior lenticonus, Macular abnormalities
• X linked - males with
  ◦ haematuria from infancy
  ◦ deafness -50% by age 15
  ◦ hypertension mid teens
  ◦ eye signs 2nd to 3rd decade of life
  ◦ ESRD in late teens, young adult – 50% by age 25
Proteinuria, nephrotic syndrome,

- Normal
- "Micro" albuminuria
- Tubular proteinuria
- Nephrotic syndrome definitions
- Mechanism of oedema

Where is it from?

- Glomerular proteinuria- albumin
  - Injury in any part of the glomerular filtration barrier
- Tubular- low molecular weight proteins (MW<40,000)
  - Failure to reabsorb by dysfunction of proximal tubule

Detecting Proteinuria

- Dipstick Measurement- Colorimetric Method
- Qualitative
- Concentration dependent
- False-positives: alkaline urine, radio-contrast
Normal values for proteinuria

- Normal protein <4mg/m²/hr (100mg/m²/day)
- Nephrotic range >40mg/m²/hr (1000mg/m²/day)
- For timed specimen, collect overnight urine (12 hr) period rather than 24 hour collection
- Collected specimen at rest and afebrile

- Difficult to collect 24h urine – but gold standard
  - Urine protein to creatinine ratio – N<22, nephrotic range >200

“Microalbuminuria”

- Some subjects have moderately increased urine albumin excretion but still do not have clinical proteinuria as detected by standard dipstix test – “microalbuminuria” – 
  “moderately increased urine albumin excretion” = 30-300mg/24h of urine alb or 20-200ug/min
- Urine alb excretion >300mg/24h = severely increased albuminuria/overt/clinical proteinuria
- Normal urine albumin/creatinine <2.5mg/mmol

Why is moderately increased albuminuria important?

- Strongly correlated with development of diabetic nephropathy
- Independent risk factor for cardiovascular disease
- in non diabetics, obesity, metabolic syndrome

Proteinuria

- Marker of glomerular injury
- Leads to progressive renal injury
- 10% of children aged 8-15 yr test positive for proteinuria by urinary dipstick at some time.

- Types:
  - ORTHOSTATIC/POSTURAL/TRANSIENT = BENIGN
  - FIXED
Haematuria and Proteinuria
- If together → significant kidney disease
- Must exclude infection
- Studies:
  - C3, C4, ANA, Albumin, FBC, Creatinine
  - ± Renal US
- Refer to Nephrology

Orthostatic/Postural Proteinuria
- Abnormally high protein excretion in upright position
- Usually < 1 gram/day
- Normal excretion when patient is recumbent (1st morning void or split urine)
- Result of altered intra renal haemodynamics, activation of RAS
- Benign, Girls>Boys
- Follow-Up: Repeat 1st morning urine yearly

Transient proteinuria
- Fever, exercise, heart failure
- Most likely due to hemodynamic alterations
- Resolves within 10-14 days of defervescence
- Resolves within 48 hours of rest from vigorous exercise
- Benign- Does not indicate underlying renal disease

Tubular proteinuria
- Low molecular weight proteins (MW<40,000) filtered and absorbed by proximal tubule – RBP, B2M
- Proximal tubular dysfunction/injury results in tubular proteinuria
  - Drugs(cisplatinum, aminoglycosides, heavy metal poisoning)
  - Cystinosis, Lowe syndrome, Dent’s disease
- Serum alb usually normal
Definitions in nephrotic syndrome

- **Nephrotic syndrome**: Oedema, uPCR ≥200 mg/mmol, 3+ protein on urine dipstick, hypoalbuminemia ≤25 g/l
- **Complete remission**: uPCR <20 mg/mmol or <1+ of protein on urine dipstick for 3 consecutive days
- **No remission**: Failure to reduce urine protein excretion by 50% from baseline or persistent excretion >200 mg/mmol
- **Initial responder**: Attainment of complete remission within initial 4 weeks of corticosteroid therapy

Definitions – cont’d

- **Steroid resistance**: Failure to achieve complete remission after 6 weeks of corticosteroid therapy
- **Relapse**: uPCR ≥200 mg/mmol or 3+ protein on urine dipstick
- **Infrequent relapse**: One relapse within 6 months of initial response, or one to three relapses in any 12-month period
- **Frequent relapse**: Two or more relapses within 6 months of initial response, or four or more relapses in any 12-month period
- **Steroid dependence**: Two consecutive relapses during corticosteroid therapy, or within 14 days of ceasing therapy

Forms of steroid resistant nephrotic syndrome in childhood

- Minimal change
- Focal segmental glomerulosclerosis
- Membrano-proliferative glomerulonephritis
- Membranous nephropathy
- Secondary chronic glomerulonephritides
  - IgA nephritis
  - Henoch Schonlein
  - Lupus nephritis
- Congenital nephrotic syndrome

Case

- A 3-year-old boy is referred to you with a 4-day history of progressive facial puffiness. There is no past history of note
- Urinalysis shows 1+ blood, 4+ protein, serum albumin 17 g/L, creatinine 40 µmol/L
- Examination shows mild to moderate periorbital oedema, BP 110/70
Question

What is the most likely diagnosis
a) Acute nephritis
b) Minimal change disease
c) C3 glomerulonephritis
d) Membranous glomerulopathy
e) Acute interstitial nephritis

Question

The patient passes little urine 24hrs after admission. His creatinine is now 110umol/L, (N 35-50), albumin 12g/L (35-45), HB 149g/L, BP 90/50, HR 95/min. He is warm and well perfused. What is the next most appropriate treatment
a) Maintenance IV fluids
b) High dose frusemide
c) 20% albumin infusion
d) Fluid restriction
e) Fluid challenge with 0.9N saline

Question

In minimal change nephrotic syndrome, which of the following best explains development of oedema
a) Reduced plasma oncotic pressure
b) Excessive sodium reabsorption
c) Increased glomerular hydraulic pressure
d) Increased circulating vasopressin
e) A combination of both reduced oncotic pressure and increase sodium reabsorption

A new way of looking at proliferative glomerulonephritis

P-GN results from 2 basic inflammatory responses:

1) the proliferation of indigenous cells of the glomerulus, (mesangial cells, endothelial cells, parietal epithelial cells, and/or infiltrating mononuclear or polymorphonuclear cells;

2) the synthesis of matrix material such as mesangial matrix, basement membrane, fibrin

Differing patterns of glomerular injury results – mesangio-proliferative, membrano-proliferative, diffuse proliferative, crescentic