Renal

GENERALISED PARENCHYMAL DISEASES REVISITED

Glomerulonephritis

Glomerulonephritis is inflammation of the glomeruli. Both kidneys are usually symmetrically affected and the disease may affect mainly the kidneys (primary GN) or may be involved as part of a systemic disease process (secondary GN). Notably, glomerulonephritis accounts for 30% of end-stage renal failure.

1. Aetiology – most types of GN result from an interaction between antibody and antigen within the glomerulus, although in the majority of cases the antigen is unknown

2. Pathogenesis – it is thought that either circulating immune complexes are trapped within the glomerulus, or more often antibody and antigen are trapped separately
   a. Antibody and antigens interact forming complexes that lead to inflammation, tissue damage
      i. Histopathological pattern depends on where immune complexes lodge and characteristics of the complexes themselves
      ii. Immune complexes are not found in some forms of GN; in these conditions other mechanisms are thought to be important (e.g. T-cell function in minimal change)
   b. Disruption in the integrity of the basement membrane allows protein and red cells to pass into the urinary space and appear in urine; severity determine the clinical syndrome
   c. GFR may also be reduced due to either glomerular infarction from crescent formation, or sclerosis of segments or complete glomeruli following necrosis 2° to inflammation. Renal tubule damage and damage to the surrounding interstitium is also important.

3. Clinical features:
   a. Nephritic syndrome – haematuria, hypertension, oedema, oliguria, proteinuria, uraemia
   b. Nephrotic syndrome – hypoalbuminaemia (<30g/L), peripheral oedema, heavy proteinuria (>3g/d) and hypercholesterolaemia; there may also be haematuria
   c. Asymptomatic proteinuria and/or haematuria (macrocytic/microcytic) ± hypertension
   d. Chronic renal failure

4. Investigations – renal biopsy is necessary to identify the histology, prognosis and plan treatment
   a. Bloods – FBC + smear (anaemia, haemolytic-uraemic syndrome), ESR (autoimmune), U&Es, creatinine (renal function), albumin, CRP, 24-hr urine (protein, CrCl, deposit), ANA (SLE), C3/C4 (reduced in active GN), ANCA (systemic vasculitides), anti-GBM antibody
   b. Imaging – ultrasound (size and scarring of kidneys, exclude other causes e.g. obstruction)
   c. Histopathology – light (LM), immunofluorescent (IF) and electron microscopy (EM)
      i. Focal – some but not all glomeruli involved
      ii. Segmental – some parts of affected glomeruli are normal
      iii. Diffuse – all parts of affected glomeruli are involved
      iv. Necrosis and/or sclerosis (segmental or diffuse or interstitial)
      v. Crescents – epithelial cell proliferation 2° to leakage of inflammatory mediators
      vi. Basement membrane thickening – subepithelial, subendothelial or mesangial

Primary glomerulonephritis:

1. Minimal change GN accounts for 90% of nephrotic syndrome in children <5 years and 30% of adults
   a. Aetiology – possibly due to abnormal T-cell clone, associated with lymphoma, Li, NSAIDS
   b. Clinical features – mainly nephrotic syndrome; hypertension, haematuria and ARF all rare
   c. Diagnosis – LM normal, IF negative, EM shows fusion of epithelial foot processes
   d. Management – 90% respond to corticosteroid therapy with proteinuria improved by 7-28d
   e. Prognosis – 25-33% become steroid-resistant, only 1% progress to end-stage renal failure

2. IgA GN (Berger disease) is the commonest cause of GN worldwide, usually affecting young males
   a. Aetiology – unknown, but strong association with alcoholic liver disease
   b. Clinical features – recurrent macroscopic haematuria with URTI; Henoch-Schonlein purpura
   c. Diagnosis – LM shows diffuse mesangial proliferation with IF for IgA and C3
   d. Management – ACE inhibitors, glucocorticoids, immunosuppressives may have a role
   e. Prognosis – good, only about 20% progress to renal failure

3. Focal segmental GS is the 2nd most common cause of nephrotic syndrome in children (3rd in adults)
   a. Aetiology – majority idiopathic, may be 2° to heroin abuse, AIDs, other proliferative GN
   b. Clinical features – nephrotic syndrome; haematuria, hypertension, renal impairment (50%)
   c. Diagnosis – LM shows segmental sclerosis, IF for C3 or IgM, EM shows foot-process fusion
   d. Management – corticosteroids, cyclophosphamide, cyclosporin; NSAIDS/ACEi for severe NS
   e. Prognosis – about 50% progress to ESRF within 10 years; 30% recurrence post-transplant

4. Crescentic (rapidly progressing) GN may be non-antibody RPGN, IC RPGN or anti-GBM disease
   a. Aetiology – vasculitis (non-antibody), idiopathic (immune complex), antibody (anti-GBM)
   b. Clinical features – renal failure (days to weeks), hypertension, pulmonary haemorrhage
   c. Diagnosis – LM shows focal necrotising GN with cellular crescents
   d. Management – high-dose corticosteroids, cyclophosphamide ± plasma exchange, transplant
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e. Prognosis – without treatment 80% develop ESRF within 2yrs; with treatment 90% survive

5. Membranous GN is the most common cause of nephrotic syndrome in adults
   a. Aetiology – idiopathic, carcinoma (10%), others (drugs, infections, vasculitides)
   b. Clinical features – nephrotic syndrome; may have mild proteinuria, hypertension or CRF
   c. Diagnosis – LM shows thickened BM, IF for IgG and C3, EM shows subendothelial deposits
   d. Management – supportive, diuretics, statins, corticosteroids ± immunosuppressives, ACEi
   e. Prognosis – untreated 50% develop ESRF (25% within 2 years), 50% just have severe NS

6. Mesangiocapillary GN usually occurs in children and young adults
   a. Aetiology – type 1 (idiopathic, systemic disease), type 2 (low C3; ‘dense deposit’ disease)
   b. Clinical features – nephrotic syndrome, may have mild proteinuria, hypertension or CRF
   c. Diagnosis: LM shows mesangial proliferation (tracks type 1), EM shows ‘double’ BM (type 2)
   d. Management – treat symptoms (nephrotic syndrome), nothing prevents/delays progression
   e. Prognosis – 50% develop ESRF within 10 years; other 50% may remit after several years

7. Familial GN
   a. Alport syndrome is the most common type of familial GN (X-linked, AD or rarely AR)
      i. Aetiology – GBM has abnormal collagen that degenerates → glomerulosclerosis
      ii. Clinical features – haematuria, slow progression to ESRF, nerve deafness (X-linked)
      iii. Diagnosis – EM shows thinning/splitting of the GBM; glomerulosclerosis if advanced
      iv. Management – treatment as for renal failure; may recur post-transplant
      v. Prognosis – males develop ESRF (16-35 years of age), females don’t (except if AR)
   b. Thin BM disease is a well-defined benign familial (AD) glomerulonephritis
      i. Aetiology – BM is thin and allows red cells to pass into the urine, degeneration rare
      ii. Clinical features – microscopic haematuria (may be macroscopic), normal function
      iii. Diagnosis – EM shows thinning and splitting of basement membrane
      iv. Management – reassurance

Secondary glomerulonephritides:
1. Diabetic glomerulopathy risk relates to the duration of diabetes mellitus (30% if >20 years)
   a. Pathology – hyperfiltration → microalbuminuria → proteinuria → nephrotic syndrome → RF
   b. Clinical features – hypertension (early feature), red cells and casts in urine deposit
   c. Diagnosis – LM (Kimmelstiel-Wilson lesions); EM (thick GBM, capillary wall, mesangium)
   d. Management – glycaemic control, lowering blood and intraglomerular pressure
   e. Prognosis – poorer prognosis than non-diabetics due to coexisting vasculopathy
2. GN due to SLE – occurs in 35-75% of SLE patients; common in other vasculitides (PAN, HSP, RA)
   a. Pathology - LM normal + IF of IgG/M/A and C3/4; focal/segmental proliferative GN, membranous GN, diffuse proliferative GN with few or >90% glomeruli with crescents
   b. Clinical features – proteinuria, haematuria, nephrotic syndrome, nephritic syndrome, CRF
   c. Diagnosis – histology cannot always be predicted from the clinical syndrome
   d. Management – depends on histology and renal impairment; cytotoxics/plasma exchange
   e. Prognosis – type 1 benign, type 2/3 unpredictable, type 4 always leads to ESRF untreated
3. Post-infectious GN
   a. Pathology – 1-3 weeks after acute β-haemolytic streptococcal infection → immune complex
   b. Clinical features – nephritic syndrome, sometimes ARF, pharyngitis or impetigo
   c. Diagnosis – low serum C3/C4, high ASO titre, LM shows mesangial/endothelial proliferation and glomerular infiltration, IF of IgG and C3 in mesangium and along the BM (seen on EM)
   d. Management – salt restriction, diuretics, antihypertensives, antibiotics, dialysis (first week)
   e. Prognosis – remits spontaneously; proteinuria and nephrotic syndrome may last 12 months
4. GN due to chronic infection
   a. Aetiology – any chronic bacterial infection (e.g. SBE, atrioventricular shunt infection)
   b. Clinical features – asymptomatic proteinuria/haematuria, signs of chronic infection
   c. Diagnosis – LM variable, macrophages in glomerulus; IF of IgG, IgM and C3
   d. Management – curing the underlying infection halts progression of disease → cure
   e. Prognosis – depends on the prognosis of the underlying infection

• Interstitial Nephritis

Interstitial nephritis is an inflammation of the non-glomerular parts of the kidney – note that this term is only used when the inflammation is the primary abnormality, and involves all parts of the kidney diffusely (i.e. not acute or chronic pyelonephritis). There is often associated fibrosis and tubular epithelial damage.
1. Clinical features:
   a. Acute interstitial nephritis – usually undetected unless progressive renal impairment is noted
   b. Chronic interstitial nephritis – silent onset of slowly progressive CRF, ↑BP uncommon
2. Aetiology:
   a. Drug toxicity – generally <1% risk per drug except methicillin (17%)
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i. Hypersensitivity to NSAIDs, penicillin, sulfonamides (cotrimoxazole), rifampicin, thiazides, frusemide, omeprazole
ii. Direct toxicity (tubular damage) – aminoglycosides, amphotericin B, heavy metals
iii. Analgesic nephropathy
iv. Radiation nephritis following radiotherapy for intra-abdominal malignancy

b. Infection – usually causes patchy inflammation with no loss of function unless recurrent or:
   i. Leptospirosis causes acute reversible decline in renal function
   ii. TB causes extensive destruction with caseating granulomas

c. Immunological – SLE and renal transplant rejection (both mainly glomerular damage)
d. Metabolic – deposition of uric acid (gout), calcium salts (nephrocalcinosis)
e. Malignant infiltration – lymphoma and leukaemia (rarely progressive), myeloma kidney (precipitation of BJP with Tamm-Horsfall protein in tubules), sarcoidosis
f. Mechanical – reflux nephropathy, calculi, ureteric fibrosis, BPH, urethral stricture, tumours
g. Idiopathic – about 10% of cases

3. Pathophysiological changes – classically chronic renal failure with the following:
   a. Hypertension – <50% of cases (c.f. 80% of glomerulonephritis)
   b. Proteinuria – <2g/day (less albumin and more tubular proteins c.f. glomerulonephritis)
   c. Impaired concentrating ability: medullary damage, post-obstruction diuresis (6-10L in 24hrs)
   d. Impaired sodium conservation – salt wasting, careful control of fluid balance
   e. Renal acidosis: distal nephron damage, ↓H⁺ excretion, ↓NH₄⁺ production, metabolic acidosis
   f. Endocrine anomalies - ↓EPO → anaemia, ↓1α-hydroxylase → renal osteodystrophy

4. Diagnosis:
   a. Presents as acute renal failure with the above changes; inactive urine sediment common (c.f. nephritis); eosinophils in urine and interstitium in acute hypersensitivity
   b. Classic triad of pyuria, haematuria and WBC casts; mild proteinuria usually present
   c. Biopsy to exclude ATN, pre-renal failure and glomerulonephritis – will show expansion of the interstitium by oedema, inflammatory infiltrate and fibrosis; negative for IgM, IgA, C3

5. Management:
   a. Identify and treat the primary cause – prednisone and antihistamines may be useful
   b. Detect and treat secondary factors that increase the degree of renal failure including water and salt depletion, uncontrolled hypertension and bacterial urinary tract infection

• Analgesics and the Kidney

Analgesic nephropathy is defined as permanent renal damage, often progressing to end-stage renal failure, caused by the prolonged ingestion of large amounts of non-narcotic analgesics in combination; specifically aspirin, paracetamol and phenacetin (since withdrawn).

1. Epidemiology
   a. Classically female (70-90%) between the age of 50-70, often with a personality disorder
   b. High incidence in Australia and parts of Belgium; low in USA, UK and NZ (<1% of ESRF)
   c. Historically incidence was much higher in Australia in the 1970s and early 1980s

2. Aetiology:
   a. Requires at least 2kg (cumulative) of mixed non-narcotic analgesic compounds; often related to chronic headaches or backaches (rarely associated with a correctable lesion)
   b. Aspirin decreases medullary renal blood flow and uncouples oxidative phosphorylation; phenacetin/paracetamol deplete intracellular glutathione leading to oxidative damage.

3. Clinical features
   a. Renal – impairment may occur with few symptoms until uraemia occurs
      i. Concentrating defects are common and occur early
      ii. Renal acidosis and salt-wasting are prominent compared to other cause of CRF
      iii. Renal artery disease and hypertension may also be present
      iv. Sterile pyuria and renal calculi may also be present
   b. Extrarenal – anaemia, gastric ulcer, severe atherosclerosis and complications, premature ageing, transitional cell carcinoma of renal pelvis and urinary tract

4. Diagnosis:
   a. IV urogram – early (wide calyces, contrast penetration into inner medulla) and late changes (papillary detachment – ring shadow, calcification; shrunked kidneys; medullary calcification)
   b. Histology:
      i. Early – necrosis of tips of loops of Henle and vasa rectae; necrosis of papillary tips (may slough off causing colic and gross haematuria)
      ii. Late – involves whole medulla with necrosis; calcification/cortical changes of interstitial fibrosis; capillary sclerosis; cortico-calyceal scarring

5. Management:
   a. Stop all analgesics – note codeine and dextropropoxyphene are safe alternatives
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b. Treat complications/renal failure, regular review to detect any new complications

**NSAIDs and the Kidney:**
1. **Acute renal failure** – 2nd most common cause of nephrotoxic ARF (after aminoglycoside toxicity)
   a. Risks – age, volume depletion, shock, sepsis, diuretics, CHF, cirrhosis, renal disease (NS)
   b. Loss of prostaglandin-mediated compensatory mechanisms to preserve GFR in ↓RBF
   c. Typically oliguric, reversible on discontinuation of the drug
2. **Interstitial nephritis** – less common than acute renal failure, usually fenoprofen
   a. Slow onset with heavy proteinuria
   b. Biopsy shows mild interstitial nephritis, minimal glomerular involvement, foot process fusion
3. **Hyperkalaemia** – decreased renin release 2° to prostaglandin inhibition leads to decreased angiotensin-II formation, aldosterone release and potassium excretion
4. **Hyponatraemia** – removal of prostaglandin inhibitory effect on ADH leads to water retention, promoting development of hyponatraemia where there are high levels of ADH (like volume depletion)
5. **Oedema** – removal of prostaglandin inhibitory effects on sodium reabsorption in the loop of Henle and cortical collecting tubule causes sodium retention; worse if there is also heart failure or cirrhosis

**Systemic Disease and the Kidney**

Diabetes mellitus carries a 20x increased risk of developing renal failure – in New Zealand about 40% of patients starting dialysis do so because of diabetic nephropathy.

1. **Pathology:**
   a. Diffuse glomerulosclerosis
   b. Nodular glomerular sclerosis (Kimmelstiel-Wilson lesions)
   c. Arteriolar hyalination
   d. Associated papillary necrosis, pyelonephritis, bladder dysfunction (autonomic neuropathy), contrast-induced renal failure, hyporeninaemic hypoaldosteronism with hyperkalaemia
2. **Pathophysiology:**
   a. Renal hypertrophy and hyperfiltration
   b. Microalbuminuria (<100mg/day, dipstick negative) – strong predictor of morbidity/mortality
   c. Hypertension – cannot be improved by glycaemia control (c.f. the other two)
3. **Natural history**
   a. Type 1 – 50% of patients after 25 years (uncommon before 10 years), associated with retinopathy, microangiopathy and neuropathy. Proteinuria >0.5g/d → renal failure in 5 years
   b. Type 2 – shorter time course after diagnosis of diabetes, ESRF more common in NZ (especially Maori and Pacific Islanders) than in Western Europe
4. **Management:**
   a. Prevention of renal failure:
      i. Glycaemic control slows the onset but does not alter the course of the disease
      ii. Blood pressure control - <120/80 alters the rate of decline of renal function
      iii. ACE inhibitors alter the course of type 1 disease over and above BP control
   b. End-stage renal failure:
      i. Survival is worse than for other dialysis patients due to other complications of DM
      ii. However, many do very well on CAPD and when transplanted
      iii. Correction of renal failure doesn’t stop progression of other diabetic complications

**Connective tissue diseases:**
1. **SLE** – glomerular lesions range from focal glomerulitis to diffuse glomerulonephritis with deposition of immune complexes and complement
   a. Patients may present with minimal signs or with nephritic or nephrotic syndrome
   b. Diagnosis – other features, low C4 and C3, ANA and anti-dsDNA antibodies
   c. Treatment – nearly all get corticosteroids; WHO class IV also get cyclophosphamide
2. **Vasculitis** – classical polyarteritis nodosa, microscopic polyarteritis, Wegener granulomatosis, Henoch-Schonlein purpura, Churg-Strauss vasculitis, Rheumatoid arthritis, systemic sclerosis
   a. Rapidly progressive glomerulonephritis most commonly, sometimes with lung haemorrhage
   b. Diagnosis aided by anti-neutrophil cytoplasmic antibody (ANCA) tests

**Gout** causes renal damage via uric acid calculi and deposition of uric acid crystals. 25% of patients who have gout get uric acid calculi; while 25% of those with uric acid calculi also have gout.

1. **Acute uric acid nephropathy** – uric acid crystals obstruct tubules and collecting system
   a. Aetiology – neoplastic disease treated with antimetabolites, heat stroke, status epilepticus
   b. Treatment – adequate hydration and allopurinol
2. **Chronic uric acid nephropathy** – uric acid thought to produce interstitial fibrosis
   a. Associated with hypertension, accelerated atherosclerosis, pyelonephritis, diabetes
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b. Routine administration to all patients with hyperuricaemia is not advocated

Autosomal dominant polycystic kidney disease is the most common inherited renal disease, and in NZ accounts for 7-9% of people on dialysis. It is less common in Maori and Pacific people, and most cases in Samoan problem relate to German ancestry.

1. Pathogenesis:
   a. PKD-1 on chromosome 16 produces polycystin 1
   b. PKD-2 on chromosome 4 produces polycystin 2
   c. Proteins are probably part of a multiprotein cytoplasmic signalling process
   d. Cyst cells produce abnormal matrix and secrete fluid, leading to cysts in 1-2% of nephron

2. Clinical features:
   a. Multiple renal cysts and renal enlargement (also cysts in liver and pancreas)
   b. Saccular cerebral aneurysms occurs in 5-10% - family history warrants CT/MRI investigation
   c. Complications – hypertension, pyelonephritis, haemorrhage, renal pain, haematuria, stones

3. Diagnosis:
   a. Most cases apparent by ultrasound by late teens
   b. Gene linkage analysis available but requires at least two affected individuals

4. Treatment:
   a. Blood pressure management
   b. Extended treatment of UTI (must penetrate to the centre of cysts)
   c. Cyst aspiration of no benefit as cysts recur

Other disorders:

1. Alport syndrome is a disease of collagen that affects the kidney, often produces nerve deafness and less commonly affects the eyes and platelets. 85% are X-linked, but AD and AR forms also occur.
   a. Aetiology – mutation in the COL4A5 gene that codes for type IV collagen
   b. Clinical features – microscopic haematuria, variable proteinuria, hypertension, renal failure

2. Amyloidosis is a deposit of amyloid, a family of proteins that polymerise to form β-pleated sheets.
   a. AL (1° amyloid) made from light chains associated with plasma cell dyscrasia and myeloma
   b. AA (2° amyloid) is made from an acute phase protein in chronic inflammatory disease
   c. Associated – light chain deposit disease, fibrillary GN, cast nephropathy, immunotactoid GN
   d. Clinical features – proteinuria (Bence Jones in AL amyloid), renal failure

3. Bacterial endocarditis can produce an immune complex GN with glomerular proliferation
   a. Clinical features – proteinuria, haematuria, sometimes hypocomplementaemia
   b. Renal emboli and mycotic aneurysms can also affect the kidney

• Renal Osteodystrophy

Renal osteodystrophy describes the skeletal complications of end-stage renal disease. Contributing factors include 1,25-(OH)2D deficiency and hyperphosphataemia with secondary hyperparathyroidism, increased levels of circulating cytokines, and aluminium accumulation in bone (old dialysates).

1. Diagnosis – laboratory parameters are rarely useful; bone biopsy best method but not usually done
2. Treatment – low phosphate diet and phosphate binder (calcium carbonate or acetate), calcium levels (to suppress PTH oversecretion), vitamin D analogues (calcitriol preferred as already activated)

Osteitis fibrosis is characterised by marrow fibrosis, increased bone remodelling, and increased amounts of osteoid and non-lamellar bone. There may be significantly elevated ALP, high PTH, hypocalcaemia and hyperphosphataemia.

Osteomalacia is characterised by low rates of bone turnover and mineralisation defects with accumulation of unmineralised osteoid. Note that it is distinct from pure vitamin D deficiency – it may be related to accumulation of aluminium and other heavy metals, which cause defective mineralisation and long-term inhibition of osteoblast function

Adynamic bone disease is poorly understood, but is essentially due to a failure of bone to remodel. It occurs mainly in ESRF patients without hyperparathyroidism – it may be related to an increase in suppressors of bone function. It is associated with increased fracture, bone pain and possibly osteopenia; there may be normal or slightly elevated ALP, near-normal PTH, and hypercalcaemia.