CLASSIFICATION OF RENAL DISEASE

• Congenital
  • Horseshoe kidney
  • Renal dysplasia
  • Renal agenesis
  • Other
• Hereditary
  • Adult polycystic kidney disease
  • Other
• Cystic diseases
  • Adult polycystic kidney disease
  • Other
• Glomerular diseases
  • Glomerulopathy/glomerulonephritis: many types, primary or secondary
  • Diabetic
  • Amyloidosis
  • Other
• Tubular and tubulointerstitial diseases
  • Infective: acute and chronic pyelonephritis
  • Drug or toxin induced
  • Urate nephropathy
  • Nephrocalcinosis
  • Cast nephropathy
  • Analgesic nephropathy
  • Acute tubular necrosis
  • Other
• Vascular
  • Changes related to renal artery stenosis
  • Embolism and infarction
  • Changes related to benign and malignant hypertension
  • Vasculitis: e.g. Wegener granulomatosis, microscopic polyangiitis, polyarteritis nodosa
  • Thrombotic microangiopathies
  • Disseminated intravascular coagulation
  • Other
• Changes related to urinary tract obstruction
  • Hydronephrosis
• Renal stones
• Neoplasia
  • Wilms tumour
  • Renal cell carcinoma
  • Transitional cell carcinoma
  • Other
• Pathology of renal transplantation

Some diseases fall into more than one group.
ARTERIONEPHROSCLEROSIS/BENIGN NEPHROSCLEROSIS
• Renal vascular and parenchymal changes related to both age and ‘benign’ hypertension (HT), frequently referred to as benign nephrosclerosis.
• In those with benign HT, the changes can more specifically be referred to as hypertensive nephrosclerosis.
• Age related changes:
  • Degenerative changes occur in arterioles with age: haemodynamic stress leads to increased endothelial permeability with deposition of plasma proteins in wall, increased extracellular matrix production and smooth muscle atrophy. The arteriole wall becomes thickened by homogenous eosinophilic glassy material (‘hyaline’) and the lumen narrowed: arteriolar hyalinosis/hyaline arteriolosclerosis. Mild medial and intimal fibrosis with replication of the internal elastic lamina occurs in small and medium arteries.
  • Small artery and arteriolar narrowing in kidneys -> chronic ischaemia ->
    • Chronic interstitial inflammation and scarring
    • Tubular atrophy
    • Focal global glomerular sclerosis or obsolescence: wrinkled collapsed mass of glomerular basement membrane surrounded by collagen in Bowman’s space.
  • Macroscopically these changes result in a smaller kidney with a thinned cortex and a granular surface, the latter due to depressed areas of atrophy with intervening non-atrophic parenchyma, sometimes with hypertrophied glomeruli.
  • Occur in >50% of those over 60 years of age without HT
  • When severe, these changes can cause chronic renal failure
• In hypertensive persons, these age related changes become more severe
  • Approx. 15% of patients with benign HT develop renal dysfunction
  • In developed countries HT is estimated to be the cause of 1/4 – 1/3 of end stage renal disease/chronic renal failure
• Proteinuria may occur with HT renal disease
• Hyaline arteriolosclerosis also occurs in diabetics, but due to different mechanisms

MALIGNANT NEPHROSCLEROSIS
Malignant/accelerated hypertension has different effects in the kidney
• Hyperplastic arteriolosclerosis (‘onion skin’ endarteritis): oedematous/myxoid intimal expansion with concentric intimal fibrosis
• Fibrinoid necrosis and thrombosis of small arteries and arterioles
• -> acute glomerular ischaemia and necrosis -> acute renal failure. The kidneys are swollen with scattered pinpoint haemorrhages

GLOMERULAR DISEASE
A wide variety of diseases can affect the glomeruli in a variety of different ways i.e. they have different pathogenesis e.g.
• Ischaemia e.g. in hypertension and diabetes
• Immunological: glomerulonephritis
• Metabolic e.g. diabetic glomerulosclerosis
• Depositions e.g. renal amyloidosis
• Hereditary

GLOMERULONEPHRITIS
• Immune mediated
• Antibody and antigen deposition around glomerular capillary basement membranes and/or in mesangium
  • Circulating antibody reacts with endogenous or exogenous antigen already within the glomerulus
  • Deposition of circulating antigen/antibody complexes
• Mediate damage via a variety of mechanisms e.g. complement activation, cytokine release, inflammatory cell infiltration
• No organisms
• Inflammatory cells not seen in all types. These types are often referred to as glomerulopathy or nephropathy rather than glomerulonephritis
• Many different types/patterns showing different light and electron microscopic changes and immunofluorescence features
  • Light microscopy: variable
    • Proliferation of cells within the glomerulus: endothelial, epithelial and/or mesangial
    • Infiltration by inflammatory cells
    • Deposition of additional mesangial matrix
    • Necrosis
    • Parts or all of glomerulus involved
    • Crescents
    • Other
• Electron microscopy: variable location and pattern of electron dense immune deposits
• Immunofluorescence: variable types and patterns of immunoglobulin and complement deposition
• Variable clinical presentation, age groups affected, outcome etc
• May cause various clinical features. Specific GNs can cause one or more of the following (sometimes mixed patterns):
  • Asymptomatic proteinuria (from increased permeability of glomerular filtration membrane)
  • Nephrotic syndrome
  • Asymptomatic haematuria
• Acute nephritic syndrome (injury to glomerular capillary walls allows leakage of blood cells +/- protein. Hyperplasia of glomerular cells and infiltration by inflammatory cells can result in impaired glomerular blood flow and filtration with renal insufficiency, hypertension and fluid retention).
• Rapidly progressive nephritis
• End stage renal disease/chronic renal failure

• Types of GN include:
  • Acute post infectious (post streptococcal) glomerulonephritis
  • Minimal change disease
  • Membranous glomerulopathy/nephropathy
  • Focal segmental glomerulosclerosis
  • Membranoproliferative glomerulonephritis
  • IgA nephropathy (diffuse mesangioproliferative)
  • Anti-glomerular basement membrane glomerulonephritis
  • Anti-neutrophil cytoplasmic autoantibody (ANCA) associated glomerulonephritis
  • Crescentic glomerulonephritis
  • Other

• Idiopathic (primary) and secondary (occurring in association with a variety of systemic diseases) forms
• Infection can precipitate a variety of patterns via immunologic mechanisms (not direct infection of glomeruli)
• Causes of nephrotic syndrome include: minimal change disease, membranous nephropathy, diabetes mellitus, renal amyloidosis, focal segmental glomerulosclerosis, other
• Causes of nephritic syndrome include: acute post-infectious GN, membranoproliferative GN, other

Examples

**Acute post-infectious glomerulonephritis**

Aetiology
• Generally follows infection with certain strains (‘nephritogenic’) of Group A β haemolytic streptococci but other organisms may also be responsible.
• Immune complexes localise in glomeruli – either form in situ or deposit from circulation. Immune complexes activate complement and other inflammatory mediators that attract inflammatory cells and stimulate proliferation of glomerular cells

Morphology
• Light microscopy: enlarged hypercellular glomeruli
  • Infiltration of neutrophils, macrophages
  • Proliferation of endothelial and mesangial cells
• Immunofluorescence: granular deposits of IgG and complement (C3) on epithelial side of glomerular capillary basement membranes and in the mesangium
• Electron microscopy: prominent subepithelial dense deposits (subepithelial ‘humps’), also subendothelial and mesangial electron dense immune deposits

Clinically
• Typically in children
• Arises 1-4 wks after a Streptococcal pharyngitis or skin infection
• Serum complement levels often low
• Typically causes nephritic syndrome: results from impaired blood flow though narrowed glomerular capillaries
  • Haematuria +/- proteinuria
  • Oliguria
  • Hypertension
  • Facial oedema
• >95% recover after several weeks with conservative therapy
• < 1% have a rapidly progressive course with the development of crescents -> acute renal failure

**Membranous glomerulonephritis**

A common cause of nephrotic syndrome in adults

Aetiology
• 85% are idiopathic
• Others arise secondary to other diseases (e.g. SLE, hepatitis B, malaria, certain cancers) or certain drugs
• All represent a form of chronic immune response to endogenous or exogenous antigens deposited on the subepithelial side of the glomerular capillary basement membranes

Morphology
• Light microscopy: thickening of the glomerular capillary wall (may not be seen early on in the disease course)
• Immunofluorescence: granular deposits of IgG and complement (C3) along glomerular capillary wall
• Electron microscopy: irregular electron dense immune deposits on subepithelial side of glomerular capillary basement membrane with intervening deposits of basement membrane material. The progressive ultrastructural changes can be divided into 4 stages.

Clinically
• Causes proteinuria which when severe results in the nephrotic syndrome
• Nephrotic syndrome
  • Massive proteinuria
  • Hypoalbuminaemia
  • Oedema
Hyperlipidaemia

Course variable. Progresses over many years to chronic renal failure in 25%

CHRONIC RENAL FAILURE

Major cause of death from renal disease.
Gradual and progressive loss of the ability of the kidneys to excrete wastes, concentrate urine and conserve electrolytes.

Clinically

- Fluid & electrolytes: dehydration, oedema, hyperkalaemia, metabolic acidosis
- Cardiopulmonary: hypertension, CCF, uraemic pericarditis
- Ca, PO_4 and bone: hypocalcaemia, secondary hyperparathyroidism, renal osteodystrophy
- Neuromuscular: myopathy, peripheral neuropathy
- Gastrointestinal: nausea and vomiting
- Haematologic: anaemia
- Dermatologic: sallow skin, pruritus
- Other

Causes of end stage renal disease: diabetes mellitus 40%, HT 26-38%, glomerulonephritis 12-16%, polycystic kidney 3%, urologic conditions 3%, other

In some cases, nephron loss due to the primary disease may lead to increased filtration and hypertrophy in remaining glomeruli, increasing their risk of secondary injury and glomerulosclerosis, leading to proteinuria and further impairment of renal function.

Macroscopic features depend on the underlying disease.

- The kidneys in chronic renal failure from HT and glomerulonephritis are generally small with granular surfaces, often with small cysts
- Chronic pyelonephritis – small kidneys, U shaped cortical scars overlying abnormal calyces
- Dialysis also affects the morphologic findings → atrophy and cysts
- Diabetic kidneys may be normal in size or enlarged, the surface is granular related to underlying vascular disease. Kidneys may be small due to hypertensive changes.
- In adult polycystic kidney disease, the kidneys are enlarged with numerous cysts.

Occasionally diagnostic features may still be seen histologically.

Irrespective of initial causes, eventually all 4 compartments (glomeruli, vessels, tubules, interstitium) become damaged – sclerosis/fibrosis of glomeruli, tubular atrophy, interstitial fibrosis and variable interstitial inflammation, thickened arterioles and small arteries

URINARY TRACT INFECTION

Cystitis

- Common
- Bladder acutely inflamed
- Usually caused by Gram negative bacteria from the gut
- Most common in women due to proximity of urethral orifice to anus, certain bacteria are able to adhere to urethral mucosa
- Patients develop dysuria, haematuria, cloudy urine

Acute pyelonephritis

- Acute supplicative inflammation of the renal tubules, interstitium and pelvis and calyces caused by infection
- Tends to primarily involve upper and lower poles – intrarenal reflux more common in these areas as the compound papillae at the upper and lower poles allow increased pressure and urinary fluid (and infection) to be transmitted into the overlying parenchyma more readily than the simple papillae (which can close under increased pressure) in the mid-regions.
- Caused by Gram negative bacilli from the gut in 85% of cases. *E. coli* most common. Other: *Proteus, Enterobacter, Klebsiella* species, *Strep. faecalis*

- 2 routes by which bacteria can reach the kidney
  - Ascending infection from the bladder is most common (95% of cases)
  - Predisposing factors include
    - Urinary obstruction e.g. benign prostatic hyperplasia
    - Instrumentation
    - Vesicoureteric reflux (due to congenital anatomic anomaly usually in males)
    - Pregnancy
    - Impaired immune system e.g. diabetes mellitus
    - Neurogenic bladder in e.g. paraplegia or diabetes
    - Renal stones
  - Haematogenous (5 % of cases)
    - From distant foci of infection e.g. in infective endocarditis
    - In the immunosuppressed or debilitated patient
    - Often with non-enteric organisms including fungi and *Staph. aureus*
  - Histologically: acute inflammation is typically in the interstitium and tubules, get tubular damage and microabscess formation. Glomerular infiltrates of neutrophils may be seen in haematogenous infection.
  - Macroscopically: kidney swollen, erythematous, microabsesses, mucosa of pyelocalyceal system is erythematous.
  - Clinically: patients develop fever, malaise (i.e. systemic symptoms), loin pain, haematuria, dysuria, cloudy urine. Creatinine generally normal unless volume depleted or pre-existing renal disease.
  - Presence of granular leukocyte casts in urine proves renal involvement in infection (casts formed in renal tubules).
Potential complications
- Papillary necrosis - mainly in diabetics and in those with urinary tract obstruction. May lead to acute renal failure
- Pyonephrosis - seen in near or total obstruction. Pus fills the renal pelvis, calyces and ureter
- Perinephric abscess: extension of infection through the renal capsule into adjacent tissue

**Chronic pyelonephritis**
- An important cause of chronic renal failure when affecting both kidneys
- Chronic tubulointerstitial inflammation and damage with renal scarring. Pyelocalyceal damage is required for diagnosis.
- Some have a history of infections but not all.
- Kidneys are small and demonstrate fine and coarse cortical scarring, the coarse scars often overly blunted or deformed calyces
- May have an insidious onset -> renal insufficiency. Polyuria and nocturia. Proteinuria may be present.
- Caused by recurrent infection, sometimes subclinical, often related to underlying obstruction and/or vesicoureteric reflux, leading to chronic inflammation and scarring

Reflux nephropathy: Uncertain if reflux itself can lead to scarring or whether concomitant bacterial infection is required.

**Nephrolithiasis**
- Stones may form anywhere within the urinary tract but the kidney is the most common site
- Affects 5-10% of people; M >F
- Some cases have a familial predisposition

**Cause and pathogenesis**
- 4 main types
  - Calcium: most common, usually a mix of \( \text{Ca}^{++} \) oxalate and \( \text{Ca}^{++} \) phosphate
    - Most related to hypercalciuria, without hypercalcaemia
    - Others related to underlying disease causing hypercalcaemia (e.g. hyperparathyroidism) or to hyperuricosuria, acting as a nucleus for the deposition of calcium, or to hyperoxaluria
  - So-called triple stones: magnesium ammonium phosphate
    - Largely follow infection by urea-splitting bacteria e.g. *Proteus* which convert urea to ammonia and thus make the urine alkaline, causing the precipitation of magnesium ammonium phosphate
    - Form some of the largest stones
  - Uric acid stones
    - Common in patients with hyperuricaemia (and gout)
    - Others may have excessively acidic urine
  - Cysteine stones
    - Genetic defect in the renal reabsorption of amino acids including cysteine

- Stones are caused by a variable combination of an increased concentration of the stone’s constituents within the urine to a level of supersaturation, changes in urinary pH and volume, the presence of factors that act as ‘nuclei’ for the deposition of crystals and the deficiency of inhibitors of crystal formation.

**Clinical course**
- May not cause any problems
- Smaller stones are more hazardous because they may pass into the ureter and cause spasm → renal colic (severe pain) and ureteric obstruction
- Larger stones more likely to stay within the renal pelvis and may cause hydronephrosis
- Haematuria
- Predisposition to infection

**Urinary Tract Obstruction**
- Increases susceptibility to infection and stone formation
- If unrelieved will lead to hydronephrosis (dilated renal pelvis and calyces) and permanent renal parenchymal atrophy (from pressure impairing blood supply in parenchyma), and chronic renal failure if bilateral

**Causes**
- Congenital anomalies
- Stones
- Prostatic enlargement (hyperplasia or malignancy)
- Other tumours obstructing ureters
- Pregnancy

Progressive dilation of pyelocalyceal system, flattening of the papillae and thinning of the parenchyma.

**Adult Polycystic Kidney Disease**
There are a number of different cystic diseases of the kidney, including congenital and inherited ones that have different appearances. Adult polycystic kidney disease is the commonest, apart from scattered small sporadic simple cysts that are very common.

- Genetic disorder inherited in autosomal dominant fashion
- A small proportion of cases arise from spontaneous mutations
- Most cases due to mutations of PKD1 gene on chromosome 16
- The kidneys develop cysts that arise from tubular epithelium that subsequently cause pressure atrophy of adjacent tissue
- Patients typically present by middle age with hypertension, chronic renal failure, loin pain, haematuria, renal infections and/or stones.
Extra-renal manifestations include intracranial berry/saccular aneurysms, colonic diverticula, mitral valve prolapse and (asymptomatic) cysts in the liver, spleen and pancreas.

RENAL CELL CARCINOMA (RCC)
- 1-3% of all solid organ cancers
- More common in males than females
- Middle age and older

Predisposing factors
- Tobacco: incidence is doubled in cigarette smokers
- Von Hippel-Lindau syndrome (hereditary)
- Other hereditary forms
- Other

Genetics
- In most cases of RCC there are abnormalities involving one allele of the VHL gene (on chromosome 3), a tumour suppressor gene

Morphology
- Usually well circumscribed lesion, 3 to 15 cm in diameter, composed of variegated yellow-grey-white tissue +/- necrosis +/- haemorrhage +/- cystic change
- May fungate through into the pyelocalyceal system or invade the renal vein
- Histologically there are various types. The most common type shows cells with abundant clear or granular cytoplasm containing glycogen (clear cell carcinoma).
- May show marked nuclear atypia and ‘sarcomatoid’ change
- Histologic grading: Fuhrman system - 4 grades

Clinical course
- Classically: loin pain, haematuria, abdominal mass
- Constitutional symptoms include fever, malaise, loss of weight
- Tumour may be silent until it reaches a large size
- RCC can cause a variety of paraneoplastic syndromes such as
  - Polycythaemia
  - Hypercalcaemia
  - Hypertension
- Commonly gives rise to metastases in the absence of local signs
- The lungs are the most common sites of metastases, followed by bone