Glomerular diseases

Lecture from pathological physiology January, 2005

Fig. Glomerular basement membrane (GBM)

Glomerular diseases (glomerulopathy)

⇒ heterogeneous group of diseases

Dividing:
a) Primary glomerulopathy
b) Secondary glomerulopathy
   – can be manifestation of systemic diseases, vascular, metabolic or genetic disorders affecting also other organs

The mechanisms for glomerular injury are complex
↓
more often are initiated by an immune response
**Immunopathologic mechanisms**

Damage of kidney depend on:
- mechanism and intensity of immune reaction
- collocation of antigens (Ag)

Mechanisms:
- Damage by immunocomplexes
- Damage by cytotoxic antibodies (Ab)
- Cell-mediated immune injury = delayed-type hypersensitivity
- Damage by complement and proinflammatory mediators

**Cytotoxic (Type II) reaction**
- antibody mediated cytotoxicity (ADCC)

These occur when antibodies interact with antigens found on cell surface

2 mechanisms of cytotoxicity:
1. Ab mediate cell destruction via mechanism ADCC (cell cytotoxicity dependent on Ab)
2. Ab directed against cell-surface antigens mediate cell destruction via complement activation

**Type III reaction – immune complex-mediated hypersensitivity**

The reaction of antibody with antigen generates immune complexes. In some cases, large amounts of immune complexes can lead to tissue damage
- They deposited in various tissues
- induce complement activation and ensuing inflammatory response

Antigens can be:
- a) Endogenous – for example DNA in SLE
- b) Exogenous – bacteria, viral, parasitical Ag

The magnitude of the reaction depends on the quantity of immune complexes as well as distribution within the wall of glomerular capillary
**Location** of immune deposits in the glomerular capillary wall

- Subepithelial
- Subendothelial
- Intramembranous

**Delayed** – type hypersensitivity (Type IV)

T lymphocytes may also recognize antigen.

When they do, a mononuclear cell infiltrate may accumulate at the site of Ag concentration and lead to the elaboration of toxic products and tissue injury.

**Four major pathogenetic forms of glomerular injury**

In non-proliferative glomerulopathy:

- Damage by antibodies
- Damage mediated by complement

In proliferative glomerulopathy:

- Damage by circulating proinflammatory cells (especially neutrophils and macrophages)
- Damage by locally activating resident cells (for example mesangial cells)

**Classification** of glomerulopathies

- Clinical: primary x secondary
- According time period: acute x subacute x chronic
- According renal biopsy: focal x segmental x diffuse
- According number of cells: non-proliferative x proliferative
- According immunofluorescence:
Pathogenic mechanisms of glomerular diseases

- **Nephritic**
- **Nephrotic**
- **Chronic glomerulonephritis**

Histologic pattern

- May not correlate with the clinical presentation
- Various histological types of glomerulonephritis

Pathogenesis of nephritic diseases

B: “Minimal changes” GN = lipoid nephrosis: some mesangial proliferation, edematous podocytes, fusion (“loss”) of their foot processes

C: Intracapillary mesangial proliferative GN proliferation of endothelia and mesangium, peeling off of endothelial cells from the GBM, duplication of GBM, “humps” formed by immunocomplexes

D: Crescentic GN: proliferation of all components (aggressive white cells, endothelium, mesangium, epitheloid and giant cells), leakage of fibrin. Hypersensitivity reaction type II or IV

E: Membranous GN Precipitation of immunoglobulins on the outer surface of the GBM (“spike” → complete incorporation of Ig into the membrane)

F: Proliferative sclerotizing GN: advanced mesangial proliferation → narrowing and destruction of capillaries
Acute glomerulonephritis (poststreptococcal GN)

- Is commonly caused by infection by certain strains of group A beta-hemolytic Streptococci (pharyngitis, pyoderma)
  - Ab against streptococci react with vimentin → immunokomplexes
- Nephritis develop after a latent period of about 2-3 weeks
- Clinical syndrome: nephritic syndrome
- Histologic pattern: intracapillary proliferation of mesangial and endothelial cells with subepithelial ("humps") and subendothelial deposits (C3, or IgG)

Postinfectious non-streptococcus glomerulonephritis

- Acute glomerulonephritis can develop also in the course of other infections:
  - Staphylococci
  - Pneumococci
  - Klebsiella pneumonia
- Staphylococci
- Herpes virus
- EBV
- Virus hepatitis B

- GN in infection endocarditis
- GN in visceral abscessus (especially lung)

Histologic pattern and clinical syndrome – similar one as in poststreptococcal GN

Focal proliferative glomerulonephritis

- Different etiology:
  - IgA nephropathy
  - Nephritis in systemic lupus erythematoses (SLE)
  - Nephritis in bacterial endocarditis
  - Henoch-Schölein purpura
**Rapidly progressive glomerulonephritis (RPGN)**

- Heterogeneous group of diseases, it is characterised by intense proliferation of glomerular/capsular epithelial cells in the form of a crescent.
- Crescent = accumulation and proliferation of extracapillary cells.
- The glomerular capillaries collapse and are bloodless, and fibrin can be identified within the capsule.
- It can stimulate proliferation of parietal epithelial cells.
- Deposits of fibrin compress the glomerula capillaries tuft (↓ GFR and destruction of glomerulus).

**Goodpastures’ syndrome**

- It is characterised antibodies against basal membrane of glomeruli (alveoelastic membrane).
- Etiology: combination of exogenous factors (smoking, infection, toxins) with genetic predisposition (HLA B7, DR2).
- Pathogenesis: GBM is composed by collagen IV with proteins (laminine, entakte, tenascine) and proteoglycans.
- Goodpastures antigen (localised in C-terminal non-collagen globular domain (NC1) of the molecule α3 chain of collagen IV).
- Formation of Ab (IgG1 – can activate complement) → damage of BM.
- Clinical manifestation: typically presents with crescentic glomerulonephritis + pulmonary hemorrhage.

**Three forms of RPGN**

- GN with creation of antibodies (IgG, IgA) against GBM (anti-GBM)
  - Linear deposits of Ig
    (+ alveoelastic BM) → Goodpastures’ syndrome
- GN with granular deposits of Ig and complement
  - Formation of crescent is complication less serious intraelastic proliferative GN (IgA nephropathy, SLE, acute GN e.g.)
- GN with ANCA antibodies
  - ANCA ab (Ab against cytoplasm of neutrophiles)
    2 forms – systemic disorders
    (Wegener granulomatosis)
    - only renal disease

**Slowly progressive glomerulonephritis**

- Group of GN called membrane-proliferative GN
- 2 forms:
  - in 1 form: ↓ levels of complements in plasma
    - subendothelial and mesangial deposits are present
    - findings: proteinuria or picture of nephrotic syndrome
  - in 2 form: activation of complement is due to nephritic factor C3
    - intramembranous deposits are present
    - findings: proteinuria or picture of nephritic syndrome (similarity as in RPGN)
Pathogenesis of nephrotic diseases

- Loss of lipoprotein lipase
- Liver lipoprotein synthesis
- Hyperlipidemia
- Intravascular oncotic pressure
- Interstitial oncotic pressure
- Hypervolemia
- Loss of potassium
- ADH
- Aldosterone
- Hypovolemia
- Proteinuria
- Filtration of proteins into interstitium
- Permeability of capillaries
- Na retention

„Minimal changes“ GN (lipoid nephrosis)

- Especially in children
- Pathogenesis ambiguous – connection with viral infections, vaccination, atopy, application some drugs (antiphlogistics etc.), Association with several HLA antigens (DRw7, B8, B12 ...)
- Finding: loss of negative charge
  (↑ permeability for some proteins – albumins)
- Histologic pattern: fusion („loss“) of foot processes of podocytes (pedicules), edematous podocytes, some mesangial proliferation
- Therapy: corticoids

Focal (segmental) glomerulosclerosis

- More serious degree
  - focal: < 50% glomeruli are affected
  - diffuse: > 50% glomerulus are affected
  - segmental: only a part of the glomerular tuft is involved
  - glomerulosclerosis: obliteration of capillary lumens
Membranous GN

- Diffuse thickness of GBM due to deposition of Ig in basement membrane
- Strong association with HLA (B8, DR3) and genes of alternative way of activation of complements (Bf)
- Often secondary etiology:
  - drugs (Au, penicilamin...)
  - tumors (especially ca GIT)
  - infection (hepatitis B)
- Clinical manifestation: nephrotic syndrome with miroscopic hematuria and sometimes hypertension
- Therapy: according etiology

Membranoproliferative (mesangiocapillary) glomerulopathy

- Is characterised by hypercellularity of the glomerular cells and basement membrane thickening
- 2 forms: classical form – proliferation of mesangial matrix with expansion to capillary walls between endothelium and BM
disease of denser deposits – non-linear accumulation of material in lamina densa of the basal membrane
- etiopathogenesis: ??? - association with infection (endocarditis, abscessus....) - genetic fators (HLA B8, DR3....)
- Clinical syndrome: nephrotic proteinuria with microhematuria, hypertension, anemia and decreased levels of the complements (C3)
**IgA nephropathy (Berger’s disease)**

- Mesangiproliferative GN with deposits of IgA, event. C3
- Etiology: - unknown, clinical manifestation is associated with infection – with latent period 2-3 days
  - association with HLA (DQ, DP)
  - T-lymphocytes produce ↑ levels of IL-2 (+ ↑ IR-2R) and they are constantly stimulate
  - ↑ production of IgA by B-lymphocytes
- Clinical manifestations: asymptomatic hematuria - nephrotic syndrome

**Chronic glomerulonephritis**

- Common terminal result of many glomerular diseases
  - („end stage kidney“)
- It is characterised by different degrees of sclerosis and proliferation

**Pathogenesis:**
- damage (loss) of nephrons
  - ↓ hyperperfusion
  - ↓ hyperfiltration
  - sclerosis of glomeruli

**Glomerulopathy in connective tissue disorders**

**Systemic lupus erythematosis**

- SLE predominantly affects women, who account for 90% cases
- The age of onset is usually between 20 and 40 years
- Many different tissues and organs may be involved (the body produces antibody against its own DNA), but renal involvement is the most significant in terms of outcome

- Histologic pattern:
  - WHO classification – normal glomerules (typ I)
  - mezangial GN (typ II)
  - focal proliferative GN (typ III)
  - diffuse proliferative GF (typ IV)
  - membranous GN (typ V)
  - glomerular sclerosis (typ VI)

**Vasculitis**

- Heterogenous group of diseases characterised by necrotising inflammation of vessels
- Etiology: primary x secondary

- Pathogenesis:
  - damage by immuno complexes
  - ANCA (pauciimmune form)
  - damage by cells (IV. typ)
**Henoch-Schönlein purpura**

- Systemic vasculitis affecting medium-sized vessels
- Especially in children and younger people
- It frequently develops post-infections
- Clinical manifestation: non-trombocytopenic purpura
  - Affect joints, serous membrane, GIT and glomeruli

  ↓
  alterations are similar to finding in IgA nephropathy

**Polyarteritis nodosa**

- Is an inflammatory and necrotizing disease involving the medium-sized and small arteries throughout the body.
- Men are more commonly affected than women
- Etiopathogenesis: usually unknown
- Clinical manifestation: variable – general symptoms + specific symptoms
  (skin, kidney, GIT, heart...)
- Histologic pattern: focal glomerular sclerosis, crescents

**Pauci-immune necrotizing GN**

**Wegener’s granulomatosis**

- Is a vasculitis leading to sinus, pulmonary and renal disease

  glomerulonephritis

  ↓

  90% of such patients have a positive ANCA
  ANCA – react with neutrophils
  ↓
  respiratory burst of phagocytic cells
  ↓
  release of free radicals
  ↓
  degranulation
  ↓
  injury to endothelial cells

**Diabetic nephropathy**

= diabetic intracapillary glomerulosclerosis (sy Kimmelstilv-Wilsonův)

Etiopathogenesis: hyperglycemia affects conformation BM and mesangial matrix

↑ renal flow and glomerular pressure (hyperfiltration)

↓ proliferation of cells

thickness GMB with expansion of mesangia

glomerulosclerosis

Clinical manifestation: latent stage - asymptomatic
incipient stage
manifest stage of diabetic nephropathy
chronic renal failure
**Schematic demonstration of running diabetic nephropathy**

- Normal state: pressure in glomerular capillaries 35 mm Hg
- Predominantly diabetic nephropathy: pressure in glomerular capillaries 45 mm Hg
- Progressive diabetic nephropathy: pressure in glomerular capillaries 45 mm Hg

- Luminal capillary
- GBM
- Glomerular filtrate
- Albumin, IgG

**Amyloidosis**

Kidney belong to organs most frequently affected by amyloidosis

AL amyloidosis – is a complication of myeloproliferative diseases (myeloma, (primary) makroglobulinemia)

AA amyloidosis – is a complication of chronic inflammatory diseases (RA, (secondary) TBC, Crohn’s disease e.g.)

Clinical manifestation: nephrotic syndrome, subsequently renal failure develops

**Hereditary nephropathies**

**Alport syndrome**
- Hereditary nephritis with deafness (X chromosome)
- Pathogenesis: congenital defect of collagen synthesis
- GMB very slight or with more layers
- GN focal (diffuse) proliferation with segmental sclerosis
  ⇒ hematuria, proteinuria or renal failure (males)

**Congenital nephrotic syndrome**
- AR heredity
- Pathogenesis: defect of synthesis of basal membrane
  - Pronounced and non-selective proteinuria
  ⇒ Nephrotic syndrome from first weeks of the life — renal failure