Glomerulonephritis

Glomerulonephritis includes a range of immune-mediated disorders that cause inflammation within the glomerulus and other compartments of the kidney[1] .

Glomerulonephritis results from a variety of immune and inflammatory mechanisms. It is often described as primary, when there is no associated disease elsewhere, or secondary, when glomerular involvement is part of a systemic disease - eg, systemic lupus erythematosus (SLE), polyarteritis nodosa. Primary glomerulonephritis may be classified according to the clinical syndrome produced, the histopathological appearance or the underlying aetiology. There is no direct correlation between the clinical syndrome produced and the pathological description.
Glomerulonephritides may be:

- Minimal change.
- Diffuse: affecting all glomeruli.
- Focal: affecting only some of the glomeruli.
- Segmental: only affecting parts of an affected glomerulus.

Many cases of glomerulonephritis result in a mild, asymptomatic illness that remains undiagnosed[2] .

Histological patterns

The commonly used pathological classification depends on light microscopy but immunofluorescence and electron microscopy provide additional information and may give clues as to the aetiology[3] .

Minimal change disease[4]

- Light microscopy is virtually normal but electron microscopy shows widespread fusion of the epithelial cell foot processes on the outside of the glomerular basement membrane. Immunofluorescence is usually negative.
- Most often presents in children aged over the age of 1 year. The incidence falls dramatically after puberty. It accounts for 70-90% of cases of nephrotic syndrome in children and about 15% of cases in adults.
- Clinical features: nephrotic syndrome with selective proteinuria; normal renal function, normal blood pressure, normal complement levels; increased risk of infections, especially urinary tract infections and pneumococcal peritonitis (therefore give prophylactic penicillin if oedematous).
- Associated with atopy in children, especially those who are HLA-DR7-positive.
- May also be related to underlying Hodgkin's disease in adults.
- Usually responds to a course of high-dose prednisolone but relapse is frequent.
- Relapsing disease may go into remission following treatment with prednisolone and cyclophosphamide or ciclosporin.
- One third of patients have one episode, one third develop occasional relapses and one third have frequent relapses which stop before adulthood.
- The use of anti-CD20 antibodies has provided long-term remission off-therapy in some patients.
- Minimal change disease does not progress to end-stage chronic kidney disease.

Focal segmental glomerulosclerosis [5] [6]

- Some of the glomeruli show segmental scarring, together with foot process fusion as in minimal change disease.
- A common cause of nephrotic syndrome in older children and younger adults; it may be associated with haematuria, hypertension and impaired renal function.

- Up to 80% of children with primary disease are resistant to treatment with steroids. If this is unsuccessful, some patients may respond to the addition of cyclophosphamide, ciclosporin, tacrolimus, mycophenolate mofetil (MMF), mizoribine, or leflunomide.
- A large proportion of steroid-resistant patients progress to end-stage renal disease.
- A variant known as 'collapsing glomerulopathy' is associated with HIV infection [7] .

Membranous nephropathy [8]

- Widespread thickening of the glomerular basement membrane occurs.
- Immunofluorescence reveals granular deposits of immunoglobulin and complement.
- Although most cases are idiopathic, it may also be secondary to SLE, hepatitis B, malignancy or the use of gold or penicillamine.
- It is more common in men.
- It is a relatively common cause of nephrotic syndrome in adults. It may present with proteinuria or nephritic syndrome, hypertension. Haematuria is rare.
- One third of patients respond to conservative treatment with diuretics, statins, ACE inhibitors or angiotensin receptor blockers, systemic anticoagulant therapy (newer direct oral anticoagulant agents or vitamin K antagonist therapy), antihypertensives, and dietary salt restriction.
- Another third respond to alternating courses of steroids and cyclophosphamide, rituximab, calcineurin inhibitors, chlorambucil, mycophenolate mofetil, or adrenocorticotropic hormone (ACTH) analogs.
- End-stage kidney disease occurs in 20-50% of patients. The remainder of those with idiopathic membranous nephropathy have a complete or partial spontaneous remission of nephrotic syndrome with stable renal function.

Mesangiocapillary glomerulonephritis (MCGN) [1]

- This is also known as membranoproliferative glomerulonephritis.
- There is proliferation of mesangial cells, an increase in mesangial matrix and thickening of the glomerular basement membrane.
- It can be subdivided according to the appearance on electron microscopy.
- It is uncommon. It may present with nephrotic syndrome or nephritic syndrome in children and young adults.
- It is associated with low levels of C3.
- Secondary forms of the disease are associated with hepatitis C with or without cryoglobulins, other chronic infections and SLE.
- Treatment is done initially with ACE inhibitors/ARBs and by controlling BP. Immunosuppression is useful if no underlying cause is found.
- A proportion of patients will eventually develop end-stage kidney disease (27.5% in one study)[9] .

Mesangial proliferative nephritis[10]

- Mesangial cell proliferation combined with matrix expansion occurs. It is most often seen in the context of IgA deposition, when it is known as IgA nephropathy. Other immunoglobulins and complement components may also be present.
- IgA nephropathy (Berger's disease) often presents with macroscopic haematuria, which may be precipitated within a few days by an upper respiratory tract infection. It is also detected as asymptomatic haematuria and/or proteinuria and can present with nephrotic syndrome.
- It is more common in males.
- There is association with HLA B35 and D4, coeliac disease, alcoholic liver disease and HIV.
- Some studies suggest that a course of high-dose prednisolone can reduce proteinuria and delay renal impairment. In patients with deteriorating renal function, immunosuppressive drugs are also often used.

- Although progression is slow, a proportion of patients (unusual in children but more common in adults) may eventually develop end-stage kidney disease (5% in one study).
- The renal lesion of Henoch-Schönlein purpura is similar to that of IgA nephropathy and this may be a variant of the same disease. 20% develop impaired renal failure. End-stage kidney disease occurs rarely (3% in one study) [11] .

Diffuse proliferative glomerulonephritis [12]

- Widespread hypercellularity occurs, caused by both infiltrating inflammatory cells and proliferation of endothelial and mesangial cells. There is generally deposition of immunoglobulins and complement around the capillary loops.
- It generally presents with an acute nephritic syndrome two or more weeks after an infection.
- Most cases are associated with SLE or IgA nephropathy secondary to streptococcal infection.
- It is rare in developed countries but post-streptococcal glomerulonephritis remains common in the developing world.
- Many other bacterial and viral causes have now been described.
- Almost all children will recover without treatment (other than antibiotics for causative bacterial infection); however, a small proportion of adults may develop renal impairment. Treatment then depends on the severity of the condition. ACE inhibitors, statins and steroids may be required. Steroids and immunosuppressive therapy may be required in more severe disease.

Focal segmental proliferative glomerulonephritis [13]

- This usually occurs secondary to systemic disease - eg, SLE, Alport's syndrome.
- Several abnormal/mutated proteins leading to loss of integrity of glomerular filtration barrier have been identified.
- HIV, parvo B19, CMV, EBV, hepatitis C and simian virus 40 have all been implicated.

- Drugs associated with the condition include drugs associated with focal segmental glomerulonephritis, heroin, interferon, lithium, pamidronate and anabolic steroids.
- There is often associated segmental necrosis of the capillary loops, which is followed by crescent formation.
- The term crescentic glomerulonephritis is used when there is an accumulation of epithelial cells and invading macrophages outside the capillary loops but within Bowman's capsule (see below).

Crescentic glomerulonephritis [14]

- This may occur as part of the evolution of certain forms of primary glomerulonephritis (eg, IgA nephropathy or mesangiocapillary glomerulonephritis); however, it is more often seen in conditions such as Goodpasture's syndrome and systemic vasculitis.
- Idiopathic crescentic glomerulonephritis is classified into the following types:
    - Type 1 - anti-glomerular basement membrane (GBM) disease: presenting with linear deposits of immunoglobulin G (IgG).
    - Type 2 - immune-complex mediated: results in granular deposits of immunoglobulin.
    - Type 3 - pauci-immune: presents with few or no immune deposits, antineutrophil cytoplasmic antibody-associated small vessel vasculitis (SVV) that may be confined to the kidney or part of a wider systemic condition - eg, granulomatosis with polyangiitis (GPA).
    - Type 4 - includes combinations of types 1 and 3.
    - Type 5 - is ANCA-negative, pauci-immune renal vasculitis (5% to 10% of cases).
- It presents with the clinical syndrome of rapidly progressive glomerulonephritis.
- Without treatment, the disease progresses to end-stage kidney disease within a few months. Prednisolone and cyclophosphamide are generally effective in patients before severe renal damage occurs. Rituximab may be useful in some patients.

- Plasma exchange is recommended in patients with advanced renal disease.
- Goodpasture's syndrome[15] :
    - Due to autoantibodies directed against the glomerular basement membrane.
    - 50% of patients also have pulmonary haemorrhage.
    - The syndrome presents with rapidly progressive glomerulonephritis, usually leading to renal failure within six months if untreated.
    - Treatment with prednisolone, cyclophosphamide and plasma exchange is generally effective as long as it is started before renal disease is advanced.
    - It is very rare for patients to relapse and the long-term outcome is good following successful treatment.

Presentation

There is a spectrum of disease, from asymptomatic urinary abnormalities to the nephritic and nephrotic syndromes[1] .

- Asymptomatic haematuria and/or proteinuria.
- Nephrotic syndrome: heavy proteinuria, hypoalbuminaemia and fluid retention.
- Nephritic syndrome: haematuria (sometimes macroscopic), proteinuria, a fall in glomerular filtration rate (GFR), salt and water retention and hypertension.
- Rapidly progressive glomerulonephritis: rapid loss of renal function, such that the patient will be in end-stage kidney disease within weeks or months.
- Chronic glomerulonephritis involves a much slower deterioration in renal function, usually over several years, accompanied by haematuria, proteinuria and hypertension.

Investigations

The investigations consist of an assessment of the severity of glomerular injury, together with a search for the cause:

- Urine dipstick and microscopy: haematuria and/or proteinuria will be found and, in some forms, red-cell casts.
- Urine protein quantification: measured in a 24-hour urine sample or by protein:creatinine ratio.
- GFR: is provided by most biochemistry laboratories as the estimated glomerular filtration rate (eGFR) but can be calculated by 24-hour creatinine clearance or from the serum creatinine by the Cockcroft and Gault formula:
    - Male: GFR = (140 - age) x (weight)/(serum creatinine x 72).
    - Female: GFR = (140 - age) x (weight) x 0.85/(serum creatinine x 72).
- FBC, ESR, CRP.
- Biochemistry: renal function, electrolytes, liver function; serum albumin low in nephrotic syndrome; high potassium, low bicarbonate and high phosphate in renal failure.
- Glucose: to exclude diabetes.
- Serum immunoglobulins, serum and urine protein electrophoresis: to exclude myeloma.
- Serum complement: low in SLE and cryoglobulinaemia and some forms of primary glomerulonephritis.
- Autoantibodies: ANA, anti-double stranded DNA, ANCA, antiglomerular basement membrane antibodies.
- HBsAg; anti-HCV; antistreptolysin O titre (ASOT).
- Radiology: renal ultrasound, CXR.
- Renal biopsy: except in the mildest cases or in nephrotic syndrome in children.

Management

Management will depend on type, severity and complications of glomerulonephritis.

General measures

- Monitoring of haematuria and proteinuria.
- Treatment of oedema with diuretics and potassium supplementation.
- Blood pressure management: establishing target blood pressures and treatment of hypertension with ACE inhibitors or angiotensin-II receptor antagonists.
- Diet: advice on protein content will depend on presence and degree of nephrotic syndrome or renal failure.
- Lipid-lowering therapy.

Specific management measures

- These are dependent on the type and degree of histological changes but include:
    - Immunosuppressive therapies, including corticosteroids, alkylating agents (eg, cyclophosphamide, chlorambucil), other cytotoxics (eg, azathioprine, mizoribine), levamisole and ciclosporin A.
    - Rituximab (a monoclonal antibody that causes the lysis of B-lymphocytes)
    - Antithrombotics, such as dipyridamole, warfarin, and aspirin therapy.
    - Intravenous immunoglobulin.
    - Dialysis.

Complications

- Hypertension may accelerate the decline in renal function so tight blood pressure control is an essential part of the management of all forms of glomerulonephritis.
- Nephrotic syndrome: for example, thrombotic episodes, pneumococcal infection.
- End-stage kidney disease.

Prognosis

- This depends on the type of glomerulonephritis but treatments for glomerulonephritis remain nonspecific, often leading to side-effects and only partly successful.
- Glomerulonephritis is a common cause of end-stage chronic kidney disease.

Further reading

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