Primary glomerular disease

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Abstract

This article reviews the clinical features, pathogenesis, investigation and management of glomerulonephritis (GN). This can occur as a primary isolated renal disease, as a manifestation of systemic diseases such as vasculitis or lupus, or secondary to drugs, infections or tumours. It is an important cause of morbidity and mortality and a potentially preventable cause of end-stage renal disease, so early diagnosis is vital to allow timely referral to specialist units where renal biopsy can be performed. Proteinuria and/or haematuria are typical findings. Pathogenesis involves cells and mediators of the immune system, including the complement pathway. Intrinsic glomerular cells, especially podocytes, are important in glomerular injury and the response to it. Schemes for appropriate investigations when GN is suspected, guidelines for referral, and strategies for investigation of proteinuria and haematuria, and for management of common forms of GN are presented. When nephrotic syndrome is present, it can lead to major morbidity and potential mortality and should be managed, irrespective of the cause, with diuretics, antiproteinuric agents, cholesterol-lowering agents and, sometimes, anticoagulants. Treatment with corticosteroids, with or without other immunosuppressive agents, is effective in many forms of GN, but adverse effects are problematic. Improved understanding of the pathogenesis of GN promises more specific forms of treatment in the future.

Keywords complement; glomerulonephritis; haematuria; kidney; nephrotic syndrome; podocyte; proteinuria; treatment

The term glomerulonephritis (GN) covers a group of conditions in which there is injury in the glomerulus, the filtering unit of the kidney. This can occur either as a primary glomerular disease, or secondary to drugs, infections or tumours (see Secondary glomerular disease, pp 513–516 of this issue).

GN can be isolated or a manifestation of renal involvement in a systemic disease (Table 1). The diagnosis of GN, and particularly its subdivision into various categories, depends on clinical features, laboratory data and histological analysis. Renal biopsy, which is undertaken in specialist centres, is a crucial element in the management of glomerular diseases.

Epidemiology of GN

Reported incidences of GN vary depending on ascertainment bias and variations in renal biopsy policies. In the UK, estimated incidences range from 17 to 60 cases per million population. Any age group can be affected, though some types are particularly common in children. GN is an important cause of end-stage renal disease (ESRD) and late diagnosis of GN remains a major problem; non-specialists can have a vital role in improving the management of GN by knowing when to suspect it, arranging appropriate investigations and making early referral to a nephrologist.[1] Proteinuria is a cardinal feature of GN and the importance of proteinuria to the generalist is emphasized by the fact that it is now also recognized as an unequivocal independent cardiovascular risk factor.[2] Proteinuria may be asymptomatic, especially at low concentration; when severe it may be associated with nephrotic syndrome, in which the patient's symptoms typically include oedema and lethargy which can be profound.

The age of the patient influences the frequency of causes of nephrotic syndrome (NS): in children under 10 years of age in the developed world, about 80% of NS is caused by minimal-change nephropathy (MCN, see below).

Studies from several countries show an increasing incidence of focal segmental glomerulosclerosis (FSGS) over the last decade.

When should glomerulonephritis be suspected?

Primary glomerular disease presents clinically with abnormalities of the urine, often with hypertension, oedema and/or impaired excretory renal function (Table 2). As routine health screening becomes more widespread and cheap, reliable urine dipstick tests more widely available, asymptomatic abnormalities of the urine will be detected more commonly.

Patients presenting with hypertension, ankle oedema, non-specific ill health or unexplained lethargy should always undergo urine testing. Protein dipsticks are semiquantitative; underlying renal disease, particularly GN, is very likely when proteinuria greater than 1+ is detected. Asymptomatic urinary tract infection does not cause proteinuria, and sending a mid-stream urine sample (MSU) to be tested for infection is not an adequate response to the finding of protein in the urine.[3] Quantification of the proteinuria and investigation of the possible causes are required. Quantification requires simple estimation of albumin:creatinine ratio (ACR) on a random urine sample; timed urine collections are now rarely used.

Casts can be identified by simple microscopy of fresh urine after gentle centrifugation: cellular casts are particularly

Systemic diseases in which glomerulonephritis may feature

- Connective tissue diseases, particularly systemic lupus erythematosus
- Systemic vasculitis
- Infective endocarditis
- Other infections, including meticillin-resistant *Staphylococcus aureus*, malaria, hepatitis B and C virus, HIV
- Drug reactions, particularly non-steroidal anti-inflammatory drugs; also gold, penicillamine
- Carcinoma, lymphoma, myeloma

Table 1

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[a] I dedicate this article to the late Momir Macanovic who co-authored the original version with me. Momir sadly died in April 2007 and I still miss him.

Presentation of primary glomerulonephritis (GN)

- Asymptomatic proteinuria
- Microscopic haematuria (occasionally macroscopic, particularly with concurrent infections in immunoglobulin A nephropathy)
- Hypertension
- Nephritic syndrome (acute GN and rapidly progressive GN) with acute onset of haematuria, proteinuria, 'active urinary sediment' with red cells, white cells, cellular casts, oliguria, hypertension, oedema, impaired excretory renal function)
- Nephrotic syndrome (heavy proteinuria >3.5 g/day, hypoalbuminaemia and oedema)
- Impaired excretory renal function (assessed by serum creatinine, or by estimated glomerular filtration rate. If severe, there may be symptoms of uraemia: nausea, vomiting, anaemia, pericarditis, hypertension, and coma

Table 2

significant because they indicate acute inflammation in the kidney, usually from GN. Dysmorphic (irregularly shaped) red blood cells (RBCs) in a fresh urine sample are suggestive of haematuria of glomerular origin. Urine analysis also provides information about the severity of glomerular disease. Heavy proteinuria, marked haematuria and/or RBC casts generally indicate more severe disease than isolated microscopic haematuria or low-grade proteinuria.

When either proteinuria or haematuria is associated with evidence of systemic disease, or there is loss of excretory renal function, referral to a nephrologist may be particularly urgent. Rapidly progressive glomerulonephritis is a medical emergency requiring urgent treatment to prevent irreversible kidney damage.

Nephrotic syndrome

NS is defined by heavy proteinuria, hypoalbuminaemia and oedema. Primary GN is an important cause of NS, although NS can also result from secondary glomerular disease, diabetic nephropathy or amyloidosis.

Urine should be tested in all patients presenting with oedema; if there is no proteinuria, it is unlikely that renal disease is the cause of the oedema. In addition to specific treatment of the underlying condition, non-specific measures remain important in the management of patients with NS (Table 3).

Pathogenesis of glomerulonephritis

Immune reactions underlie GN, with contributions from cellular immunity (T lymphocytes, macrophages), humoral immunity (antibodies, immune complexes, complement) and other inflammatory mediators (including the coagulation cascade). In some cases, the target of the immune response is known (e.g. when GN complicates infections or tumours). In many cases, the target is unknown and an autoimmune aetiology is suspected.

As in other autoimmune conditions, primary GN is thought to result from the combination of genetic susceptibility and an environmental precipitant.[4] The genetic factors typically include genes involved in control of the immune response, particularly the major histocompatibility complex human leucocyte antigen (HLA) genes, although membranous nephropathy (see below) is a special case in this regard. The environmental precipitants include drugs, chemicals or infectious agents. Known predisposing factors are considered in more detail below. The role of immune mechanisms in the pathogenesis of GN is indicated by the presence of circulating autoantibodies and/or abnormalities of serum complement, and glomerular deposition of antibodies, immune complexes, complement and fibrin.

The complement system in glomerulonephritis

The association of abnormalities of the complement system with renal disease is well established. Initial observations included alterations in the serum concentration of specific complement components and/or glomerular complement deposits. Recent advances have highlighted new pathogenetic mechanisms.[5]

Hypocomplementaemia is used as a diagnostic marker and for monitoring treatment response in some forms of GN. The complement components most frequently measured in clinical practice are C3 and C4. Chronic bacteraemic states, poststreptococcal GN or lupus nephritis are frequently accompanied by reduction of the classical pathway activation protein C4 along with C3. In lupus nephritis, the extent of hypocomplementaemia can be useful for monitoring disease activity non-invasively. In mesangiocapillary GN (MCGN, see below), the pattern of complement depletion differs between the different subtypes and is useful in diagnosis.

Glomerular deposits of complement in GN, especially C3, can be visualized by immunohistochemistry. Complement deposits may be dominant (as in MCGN) or associated with immunoglobulin deposits (as in many other forms of GN).

Non-specific measures in the management of people with nephrotic syndrome

- Oedema can be reduced by salt restriction and diuretics; water immersion may be effective for intractable oedema
- Hypertension should be treated using angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), which have additional antiproteinuric effects and delay the progression of renal disease
- Patients usually have hypercholesterolaemia, which should be treated with a statin since dietary measures alone are usually ineffective
- There is a predisposition to infection, partly because of associated hypogammaglobulinaemia; also, cellulitis is common in oedematous tissues. Consequently, there should be a low threshold for administration of systemic antibiotics and vaccination against encapsulated bacteria
- A prothrombotic state is present, so disproportionate limb swelling, breathlessness, chest pain or haemoptysis should raise the suspicion of thromboembolism and a need for systemic anticoagulation. Renal vein thrombosis is a particular problem in patients with nephrotic syndrome; it may be silent or may cause flank pain, macroscopic haematuria or deterioration in excretory renal function

Table 3