EDITOR'S PICK

Our understanding of pathophysiology across the continuum of renal diseases is rapidly increasing, not only in terms of rare renal disease, but also in relation to more common diseases. Complement activation is associated with a wide number of kidney disorders, and recent advances in this area of research mean that it is quickly becoming a key target for treatment. As the range of available treatments for glomerulopathies widens, it becomes more and more important that both renal pathologists and general practitioners have the most up-to-date knowledge available at their fingertips. This is a niche that is well filled by the following paper by Dr Caliskan, who provides a great summary of a range of complement pathway associated glomerulopathies.

COMPLEMENT PATHWAY ASSOCIATED GLOMERULOPATHIES

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ABSTRACT

The complement system causes kidney injury in a variety of different diseases, and clinical evaluation of the complement system is an important part of the diagnostic workup of patients with glomerulonephritis. In cases of ongoing, uncontrolled complement activation, the kidney is susceptible to complement hyperactivation, and thrombotic microangiopathy associated kidney injury can occur. Two principle modes of complement-mediated kidney injury have been proposed: classical pathway mediated injury in immune complex diseases and/or alternative pathway mediated renal injury causing atypical haemolytic uraemic syndrome (aHUS) and C3 glomerulopathy in patients with abnormalities in alternative pathway regulation. Recent advances have also provided new insights into the pathogenesis of glomerular and tubulointerstitial injury associated with aberrant complement activation. Complement inhibition is effective for treatment of aHUS, and there is growing evidence of the favourable effect of the anti-C5 monoclonal antibody eculizumab. Measurement of *ex vivo* serum-induced endothelial C5b-9 deposits is supposed to be a sensitive tool to monitor complement activation and eculizumab effectiveness. Although understanding the role of the complement system in the pathogenesis of many kidney diseases is improved, there is not a simple algorithm for identifying which patients should be treated with complement inhibitors or for how long complement inhibition should be continued.

Keywords: Atypical haemolytic uraemic syndrome (aHUS), complement system, C3 glomerulopathy (C3G), eculizumab, glomerular diseases.

INTRODUCTION

Complement activation plays a major role in several renal pathophysiological conditions, and the spectrum of complement system associated renal diseases is constantly expanding.[1] Two principle modes of complement-mediated kidney injury have been proposed: classical pathway mediated injury

in immune complex diseases and/or alternative pathway mediated renal injury causing atypical haemolytic uraemic syndrome (aHUS) and C3 glomerulopathy (C3G) in patients with abnormalities in alternative pathway regulation.[1,2] Recent advances have also provided new insights into the pathogenesis of glomerular and tubulointerstitial injury associated with aberrant complement activation.[1,2]

The Complement System

The main effector mechanisms of complement activation are: recruitment of immune cells to sites of infection, labelling of the invading pathogens via opsonisation for uptake and destruction by phagocytes, and/or direct lysis of susceptible pathogens.[3] There are three pathways recognised for complement activation: the classical pathway, the alternative pathway, and the more recently discovered lectin pathway.[3] All three pathways converge to cleave complement component C3, which subsequently initiates activation of the terminal complement pathway and formation of the membrane attack complex (MAC) (Figure 1). In order to prevent damage to self-tissues, the complement system contains membrane-bound and fluid-phase proteins that regulate complement activation. They act by promoting decay of the convertase complexes, being cofactors for the enzymatic degradation of the active proteins, and by preventing the assembly of the MAC. An abnormal functioning of the regulatory system, due to either genetic or acquired causes, can shift the balance between regulation and activation towards the latter and lead to complement system associated tissue injury.[1-3] This kind of imbalance occurs on susceptible surfaces that lack complement regulators or do not support the binding of such regulators that normally occur on host cells.

The Complement System and Glomerular Diseases

The complement system is involved in the pathogenesis of kidney disease as a key mediator (Table 1).[4] Activation of complement can cause direct glomerular injury in glomerulonephritis characterised by immune complex deposition, and facilitates the recruitment of leukocytes into the glomerulus.[5] There is also growing evidence that activation of plasma complement proteins leaking into the tubular lumen during proteinuria, followed by strong activation of locally synthesised complement, leads to progressive tubulointerstitial damage.[4] The tendency of the kidney for complement system associated injury is incompletely understood. The following reasons are suggested: the presence of the fenestrae in the glomerular basement membrane (GBM) continuously exposing the acellular subendothelial tissues to complement activators, a lower baseline expression of complement regulators, and/or differences in the composition of the glycocalix.[5] Complement activation products can be found in the urine of patients with a wide variety of proteinuric diseases, and proteinuria provides a source of complement proteins to a host cell surface that is unable to control activation.[4]

Alternative Complement Pathway Associated Glomerulopathies

In recent years, the identification of disease-causing mutations and genetic variants in complement regulatory proteins has brought up the concept of alternative complement pathway-associated glomerulopathies (ACPAG). C3G and aHUS are the main disorders characterised by excessive activation of the alternative complement pathway. aHUS is characterised by microangiopathic haemolytic anaemia, low platelet count, and acute renal failure.[1] A similarly rare disease entity termed 'C3G' is characterised by isolated C3 deposition in glomeruli without positive staining for immunoglobulins and immunofluorescence.[1,3] Although the impact of family history and consanguineous unions on the development of ACPAG in different populations is unknown, there is ample evidence for familial aggregation of aHUS and C3G cases.[1,2,6,7] Genetic and functional studies have demonstrated that mutations and/or autoantibodies affecting proteins implicated in regulating complement biology are central to these diseases' pathophysiology.[6,7]

Membranoproliferative Glomerulonephritis - C3 Glomerulopathy

Membranoproliferative glomerulonephritis (MPGN) denotes a general pattern of glomerular injury characterised by an increase in mesangial cellularity and matrix with thickening of glomerular capillary walls. This is secondary to subendothelial deposition of immune complexes and/or complement factors, cellular entrapment, and new basement membrane formation.[8] Recently, improved understanding of the role of the alternative complement pathway in MPGN has illuminated the field and led to a paradigm shift in the disease classification.[2,8] MPGN has now been reclassified into immunoglobulin-

mediated disease (driven primarily by the classical complement pathway) versus non-immunoglobulin-mediated disease (fuelled by the alternative complement pathway overactivity).[2,8,9] C3G is a unifying description of glomerular changes, particularly of glomerular deposits of C3 without immunoglobulins that represent the hallmark of alternative pathway dysregulation through inherited or acquired defects.[9-11] C3 glomerulopathies encompass dense deposit disease (DDD) and C3 glomerulonephritis (C3GN).

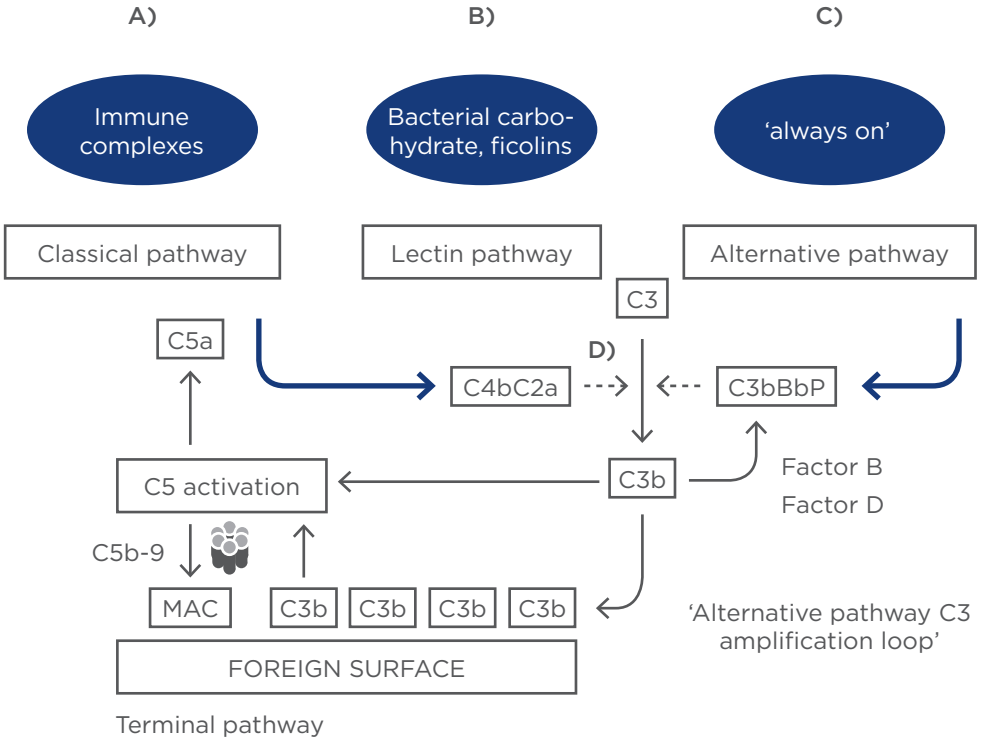

Figure 1: Activation of the complement system.

There are three pathways recognised for complement activation: classical, alternative, and lectin pathways. The classical and lectin pathways are similar, differing only in the initiator molecular complexes and the triggering signals. a) Complement C1q in association with two molecules of each of the serine proteases C1r and C1s makes the initiator complex of the classical pathway. The C1qrs complex is activated on binding to the antigen–antibody complex. b) The lectin pathway is initiated upon recognition of certain sugar patterns on surfaces of microbial pathogens by the broad-spectrum carbohydrate recognition molecules of mannose binding lectin, ficolins, or collectin-11. Binding of recognition complexes from either classical or lectin pathways to their target structures leads to activation of the attached serine proteases: C1r/C1s and MASP-1/MASP-2, respectively. The activated serine proteases C1s and MASP-2 cleave C4 into C4a and C4b. C4a is released into the fluid phase, whereas C4b attaches to the target surface. C2 binds to the attached C4b and is cleaved by C1s or MASP-2 releasing C2b into the fluid phase, whereas C2a remains attached to C4b. The resulting complex C4b2a represents the C3-convertase of the classical and lectin pathways then activates C3. c) The alternative pathway remains constitutively active, as a result of spontaneous low-level hydrolysis of the internal thioester bond of C3 to C3(H2O) in a process known as 'tick-over'. The cleavage of C3 allows the binding of the C3(H2O) to plasma protein Factor B, rendering it susceptible to cleavage by Factor D to Ba and Bb. This produces a limited amount of the fluid phase alternative pathway C3-convertase (C3[H2O]Bb) that is able to cleave C3 into C3a and C3b. C3-convertase cleavage of additional C3b and formation of C3bBb forms an amplification loop leading to the exponential production of additional C3 convertase. d) The C3 convertase cleaves C3 resulting in assembly of the C5 convertase and sequential binding of C6, 7, 8, and 9 to form C5b-9, the membrane attack complex (MAC), which inserts into target membranes, forming channels that disrupt membrane function and lead to lysis of target cells. Complement activation also results in production of the small, biologically active anaphylatoxins: C3a and C5a.

Table 1: Complement pathway-related glomerulopathies.

Alternative complement pathway associated glomerulopathies
Membranoproliferative glomerulonephritis – C3 glomerulopathy Atypical haemolytic uraemic syndrome
Other complement-associated glomerulopathies
Anti-glomerular basement membrane glomerulonephritis Anti-neutrophil cytoplasmic antibody-associated vasculitis C1q nephropathy Focal segmental glomerulosclerosis IgA nephropathy Lupus nephritis Membranous nephropathy Post-infectious glomerulonephritis

IgA: immunoglobulin A.

Although DDD and C3GN are morphologically distinguishable by the appearance and location of deposits on electron microscopy, these diseases are now considered to be part of the same aetio-pathological spectrum.[9-11] However, adult patients with DDD appear to have more aggressive disease and worse outcomes compared with C3GN.[12] Distinguishing C3G from immunoglobulin-mediated MPGN, and also further differentiation between DDD and C3GN may help for treatment algorithms and long-term prognostication. Complement system associated mutations can be found in patients with C3G. Examples include familial DDD with C3 mutation and familial C3GN with mutations in the complement factor H related (CFHR) genes.[13,14] The treatment algorithm for C3G is not well established yet. The efficacy of the C5 inhibitor eculizumab is tested in patients with persistent C3G under immunosuppressive therapy, and some patients responded to this treatment.[15] Factors affecting response to therapy are poorly understood, although acute lesions and high circulating MAC levels have been proposed to indicate higher chances of response to therapy.[15] The efficiency of eculizumab in rapidly progressive or crescentic C3G has also been reported recently.[16] However, eculizumab for the treatment of patients with C3G, or prevention of recurrence in a transplanted kidney is still outside the approved indications. Results of ongoing prospective studies of eculizumab in C3G are expected.[17,18]

Although previous studies reported a failure in response to glucocorticoid, mycophenolate mofetil, and rituximab therapy,[15,19] a recent study showed that immunosuppressive treatments, particularly corticosteroids plus mycophenolate mofetil, are found to be beneficial in C3GN.[20] Soluble CR1, a potent regulator of complement activity, is another novel therapeutic agent, and its membrane-bound form inhibits the conversion of C3 to C3b and promotes the breakdown of active C3b. A recent study suggested the effectiveness of soluble CR1 as a treatment for DDD and C3GN.[21]

Atypical Haemolytic Uraemic Syndrome

aHUS is an extremely rare disease and the annual incidence is about 0.5–2.0 per million adults and 3.3 per million children or adolescents. A differential diagnosis among the different forms of HUS is often not feasible based only on age of onset or clinical symptoms. HUS caused by *Escherichia coli* strains that produce Shiga toxins (STEC-HUS) largely predominates in infants and children aged between 6 months and 5 years, but may occur at any age. The presence of diarrhoea, a characteristic symptom of STEC-HUS, cannot be used to differentiate between STEC-HUS and aHUS because approximately one-third of patients with aHUS experience diarrhoea.[22,23] Extra-renal findings including cardiac and neurological abnormalities present in up to 20% of patients, and pancreatitis and/or hepatitis have also been reported.[22,23] Signs and symptoms of renal failure at presentation can include haematuria, oedema, hypertension (malignant in up to 8%), and electrolyte abnormality.[22] Most of the children (59%) and adults (81%) require dialysis at presentation.[23] The clinical presentation of aHUS associated with the coagulation protein, diacylglycerol

kinase epsilon (DGKE), is very similar to that of complement-mediated aHUS, although all aHUS patients associated with DGKE present in the first year of life.[24,25]

Laboratory evidence of haemolysis, thrombocytopenia, and renal failure is present in the overwhelming majority of patients. Serum C3 levels may vary during acute versus chronic disease, but are low in up to 35.9% of patients,[22] occurring most frequently in the presence of a CFH gene mutation. Historically, the onset of aHUS in only 40–60% of aHUS patients has been explained by mutations in genes encoding complement-related proteins, and 25–30% of these mutations were CFH mutations.[6,26] Studies focussed on aHUS have shown that mutations in CFH, complement factor I (CFI), membrane cofactor protein (MCP), thrombomodulin (THBD), and in genes encoding complement activators CFB and C3 as well as copy number variations in the CFHR gene cluster predispose patients to aHUS. Anti-factor H antibodies have also been shown in patients with aHUS. These antibodies bind to short consensus repeats, thus reducing the CFH activity.[27] Reduction in MCP expression is reported in >80% of cases with a mutation in this gene.[28] Genetic disorders are rarely related to CFI.[29] THBD mutations with hyperactivity have been found in only 3–5% of patients.[30] The role of non-complement related mechanisms and genetic variations as the deficiency of DGKE encoded by the DGKE gene in the aetiology of C3G and aHUS has been reported in recent studies.[7,24] It has been proposed that lack of DGKE causes enhanced signalling through arachidonic acid containing diacylglycerols and results in a prothrombotic phenotype, or may cause an enhanced activity of TRPC6 in the podocyte causing dysfunction of glomerular permselective properties.[24]

Despite the recent progress in understanding the pathophysiology of the ACPAG, there are few and inadequately validated clinical tools available for risk stratification, prediction of exacerbations, identification of autoimmune forms and selection of treatment options, and monitoring of drug response in aHUS and C3G.[31] However, Noris et al.[32] developed an *ex vivo* test evaluating the *ex vivo* serum induced C5b-9 endothelial deposits that might be a sensitive tool to monitor complement activation and eculizumab effectiveness.[32] Although STEC-HUS is characterised by full recovery in >80% of patients, patients with aHUS have a poorer prognosis. The majority of patients need dialysis at admission, and until very recently, half of all patients never recovered kidney function.[1,6] aHUS patients with end stage renal disease (ESRD) also have a 60% risk of disease recurrence in the allograft; this almost always (in 90% of cases) leads to graft loss of the affected kidney.[33] The risks of post-transplantation disease recurrence are best predicted in patients harbouring pathological mutations in known complement-associated genes. Gene discovery studies also showed that patients with mutations in DGKE carry a very low risk of post-transplantation disease recurrence.[6] Recently, the introduction of the anti-C5 monoclonal antibody eculizumab as a treatment has dramatically improved the prognosis for these patients.[34,35] Effectiveness of eculizumab was shown not only in a progressive group but also in a group of patients who required chronic plasma exchange.[35] In an open-label, uncontrolled trial, eculizumab was effective in >80% of patients in controlling haemolysis, improving renal function, and allowing the withdrawal of plasma therapy.[35] Undoubtedly, current treatment guidelines will prominently feature eculizumab treatment and suggest that treatment should be started early.

Other Complement Associated Glomerulopathies

Anti-Glomerular Basement Membrane Glomerulonephritis

Anti-GBM disease is a rare but life-threatening autoimmune disease, which clinically manifests rapidly progressive glomerulonephritis with or without pulmonary haemorrhage. In the renal biopsy of patients, linear deposition of Immunoglobin G (IgG) is often accompanied by C3 deposits, as well as a linear or granular staining pattern on the glomerular capillary wall, which indicates that complement activation is involved in the kidney injury.[36] Recently, the complement system has been shown to be activated via both the alternative and classical pathways in the kidneys of human anti-GBM disease.[37] The inflammatory response through C5a activation and/or the cell lysis effect of C5b-9 are enhanced in patients with anti-GBM glomerulonephritis.[36]

Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

Several authors documented the involvement of complement in anti-neutrophil cytoplasmic antibody (ANCA) glomerulonephritis.[38,39] Chen et al.[38] documented C3 deposits in the glomeruli of

patients with high levels of proteinuria and poor renal function. C5-9, C3d, and CFB were also reported in biopsies from patients with myeloperoxidase (MPO)-ANCA-associated pauci immune glomerulonephritis. Xing et al.[39] observed that C4d was negative in biopsies of patients with MPO-ANCA glomerulonephritis. These studies suggest that this model of glomerulonephritis requires the activation of the alternative pathway, not the classical or the leptin pathways. Further studies in patients with active ANCA-associated vasculitis documented high levels of C3a, C5a, soluble C5b-9, and Bb.[40] Recently, other authors have shown that the C5a specific receptor (C5aR) expressed on neutrophils is involved in the pathogenesis of ANCA-induced glomerulonephritis.[41] Therefore, targeting the C5a-C5aR receptor interaction in such patients might represent a therapeutic strategy.[42] A clinical trial to evaluate the safety and efficacy of an inhibitor of the C5a receptor (CCX168) is ongoing and a short-term analysis reported promising results.[42]

C1q Nephropathy

C1q nephropathy is characterised by the C1q binding to poly-anionic substances (DNA, RNA, viral proteins) or to C1q receptors. Some authors suggested that C1q nephropathy is a subgroup of primary focal segmental glomerulosclerosis (FSGS). In histopathological evaluation, C1q nephropathy is characterised by the presence of noticeable C1q immune deposits in glomeruli with no evidence of systemic lupus erythematosus (SLE) or MPGN Type I.[43]

Focal Segmental Glomerulosclerosis

The pathogenesis of FSGS remains unclear, but IgM and C3 deposits are commonly observed in the affected glomeruli.[44] Mutations in CFH and C3 have been described in cases of FSGS,[45] and a murine model of IgG-initiated FSGS in decay accelerating factor-deficient mice[46] supports a role for complement dysregulation in some cases. Complement inhibition has not been carefully studied as a therapy for FSGS.

IgA Nephropathy

IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis. The disease is characterised by mesangial deposition of polymeric IgA1. A large number of studies established that increased levels of circulating galactose-deficient IgA1 in association with the production of unique anti-glycan antibodies leads to the formation of pathogenic IgA1 containing circulating immune complexes that are deposited within the mesangium, leading to activation of mesangial cells and thus glomerular damage. Complement components including C3, C4d, C5b-9, properdin, factor H, C4BP, and mannose binding lectin (MBL) are deposited within the glomerulus in IgAN, which has been known for some time.[47,48] The alternative pathway has a primary role in 75% of cases.[49] These biopsies show colocalisation of polymeric IgA1, C3, and the MAC in the absence of other immunoglobulins, C1q, C4, or MBL. In 25% of biopsy specimens, the presence of glomerular IgA1 and C3 is associated with MBL and MBL-associated serine protease 1 (MASP-1) deposition. MBL binds to the abnormally galactosylated region of the IgA1 through its carbohydrate binding domain, resulting in complement catabolism through the lectin binding pathway. The presence of MBL and MASP-1 is associated with disease severity and poor histological prognostic features.[50]

Table 2: Key aspects of complement-associated glomerulopathies.

The kidney is a susceptible organ to abnormal regulation of complement
Major complement dysregulation related renal pathologies are: • aHUS (endothelial complement activation) • C3Gs (C3 glomerulonephritis, dense deposit disease, CFHR5 nephropathy)
Eculizumab is the first complement inhibitor and is effective in aHUS, although resistance can occur
Ex vivo serum-induced endothelial C5b-9 deposits are a sensitive tool to monitor complement activation and eculizumab effectiveness
Mycophenolate mofetil + steroid treatment can be an option for C3G treatment
There are ongoing studies evaluating the new complement inhibitors (TCR1, anti-C5a, lampalizumab, compstatin [APL-1 and APL-2])

CFHR5: complement factor H related 5; aHUS: atypical haemolytic uraemic syndrome; TCR1: T cell receptor 1; C3G: C3 glomerulopathy.

A recent genome-wide association study identified a major susceptibility locus for IgAN within the gene encoding CFH.[51] A common deletion in the regulators of complement activation cluster at 1q32, which incorporates the genes (CFHR3 and CFHR1) encoding factor H-related protein 3 and 1, has been shown to protect against IgAN,[51] possibly by reducing the ability of CFHR proteins to inhibit the regulatory function of CFH.[52] It thus seems possible that complement inhibition might be beneficial in the treatment of IgAN and in particular the crescentic form with rapidly progressive glomerulonephritis, which has a poor prognosis. The efficiency of eculizumab in a patient with Henoch–Schönlein purpura and crescentic IgAN has been recently reported.[53]

Lupus Nephritis

Proliferative lupus nephritis is classically associated with the 'full house' immunology of glomerular antibody and complement deposition in combination with peripheral consumption of the classical complement proteins. Deficiencies in the early components of the classical pathway (C1q, C1r, C1s, C2, and C4) predispose to the development of SLE.[54] While heritable mutations of C1q leading to deficiency are rare, deficiency due to excessive complement activation because of interaction with immune complexes is common, and low C1q levels are associated with active disease.[55] C1q antibodies are present in one-third of patients with SLE and are associated with lupus nephritis, sensitivity, and a specificity of >90%.[56] The generation of these autoantibodies may be precipitated by the existence of C1q on apoptotic debris that is not removed in a timely fashion. The alternative and the lectin pathways also appear to play a role in the progression of glomerular damage.[57] Patients presenting with the glomerular deposition of properdin, a positive regulator of the alternative pathway, and patients with MBL/L-ficolin, showed increased urinary protein excretion.[57] Taken together, glomerular deposition of C1q in the context of immune complexes, complement activation, and functional Fc gamma receptors appear to be necessary to cause renal damage in lupus nephritis.

Membranous Nephropathy

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in Caucasians and is characterised by the immune deposits between the lamina rara externa of the GBM and the podocyte. According to the latest studies, M-type phospholipase A2 receptor (PLA2R) located on podocytes has been identified as the target antigen in idiopathic MN. The predominant anti-PLA2R IgG subclass activates the alternative or the MBL pathway.[58] This is confirmed by some studies documenting glomerular MBL and C4b deposition in MN.[58] In human secondary MN, C1q, C3, C4, CFB, MBL, and C5b-9 are typically present and co-deposited with IgG, suggesting that the lectin and alternative pathways could play the relevant role.[58] Terminal complement activation causes insertion of the MAC into the podocyte cell membrane. Podocyte apoptosis may result from direct mechanical injury following MAC insertion or be secondary to the toxic effects of injury related chemicals.[58] Detachment of podocytes from the GBM and failure of podocyte proliferation also contribute to the onset of proteinuria and are mediated by the complement cascade.[58]

Post-Infectious Glomerulonephritis

Post-infectious glomerulonephritis, classically after *Streptococcus pyogenes* infection, is characterised by proliferative glomerulonephritis and deposition of C3 with or without immunoglobulins.[59] Although the majority of patients achieve complete remission of the associated nephritic syndrome, some experience delayed resolution or chronic glomerulonephritis, resulting in ESRD. A recent study carried out on 11 patients at the Mayo Clinic found multiple underlying causes of alternative pathway dysregulation in these chronic patients, including mutations in CFH or CFHR5 and/or the presence of C3 nephritic factors.[59]

SUMMARY

The complement system causes kidney injury in a variety of different diseases, and clinical evaluation of the complement system is an important part of the diagnostic workup of patients with glomerulonephritis (Table 2). Complement inhibition is effective for treatment of aHUS, and complement inhibitors are likely to be tested in other complement pathway associated glomerulopathies in the future. Although understanding the role of the complement system in the pathogenesis of many kidney diseases has improved, there is not a simple algorithm for identifying which patients should be treated with complement inhibitors or for how long complement inhibition should be continued.

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