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C3 glomerulopathy — understanding a rare complement-driven renal disease

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R.J.H.S. researched data for the article, made substantial contributions to discussions of the article content, wrote the initial draft of the manuscript, and participated in review or editing of the manuscript before submission. G.B.A., C.M.N,, D.K., F.F. and G.R. had primary responsibility for the section on treatment; A.M.B., M.J. and J.V.d.V. had primary responsibility for the section on the glomerular microenvironment; J.D.L., V.F.-B., M.N., S.R.d.C., M.C.P. and P.F.Z. had primary responsibility for the sections on complement, genetics and autoantibodies; S.S., H.T.C. and V.D.D'A. had primary responsibility for the section on pathology. All authors reviewed, edited and approved all drafts of this paper.

Competing interests

R.J.H.S. declares that he is Director of the Molecular Otolaryngology and Renal Research Laboratories (which provides genetic and functional testing for complement-mediated renal diseases). G.A. declares that he acts as a consultant for Achillion, Alexion, Chemocentryx and Omeros, and has received research grants from Achillion and Chemocentryx. H.T.C. declares that he acts as a consultant for Alexion and Achillion. J.L. declares that he is the founder of Amyndas Pharmaceuticals, is named as an inventor on patents or patent applications describing the therapeutic use of complement inhibitors (some of which are being developed by Amyndas Pharmaceuticals), and is the inventor of the compstatin analogue licensed to Apellis Pharmaceuticals termed 4(1MeW)7W (also known as POT4 and APL1) and pegylated derivatives such as APL2. M.N. declares that he has received honoraria for lecturing and participation in advisory boards from Alexion Pharmaceuticals and has received research grants from Chemocentryx and Omeros. M.C.P. declares that he has received research grants from Achillion, Alexion and Ra Pharma and has acted as a consultant for Achillion, Alexion, ChemoCentryx and Ra Pharma; G.R. declares that he acts as a consultant for Alnylam, Boehringer Ingelheim, Handok, Hoffmann–La Roche and Janssen Research and Development (he has not accepted any personal remuneration from Alnylam or Hoffmann–La Roche; this compensation is used to support his research and educational activities). C.M.N. declares that he is Associate Director of the Molecular Otolaryngology and Renal Research Laboratories. All other authors declare no competing interests.

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Abstract

The C3 glomerulopathies are a group of rare kidney diseases characterized by complement dysregulation occurring in the fluid phase and in the glomerular microenvironment, which results in prominent complement C3 deposition in kidney biopsy samples. The two major subgroups of C3 glomerulopathy — dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) — have overlapping clinical and pathological features suggestive of a disease continuum. Dysregulation of the complement alternative pathway is fundamental to the manifestations of C3 glomerulopathy, although terminal pathway dysregulation is also common. Disease is driven by acquired factors in most patients, namely autoantibodies that target the C3 or C5 convertases. These autoantibodies drive complement dysregulation by increasing the half-life of these vital but normally short-lived enzymes. Genetic variation in complement-related genes is a less frequent cause. No disease-specific treatments are available, although immunosuppressive agents and terminal complement pathway blockers are helpful in some patients. Unfortunately, no treatment is universally effective or curative. In aggregate, the limited data on renal transplantation point to a high risk of disease recurrence (both DDD and C3GN) in allograft recipients. Clinical trials are underway to test the efficacy of several first-generation drugs that target the alternative complement pathway.

Introduction

The term C3 glomerulopathy was adopted by expert consensus in 2013 to define a group of rare kidney diseases driven by dysregulation of the complement cascade[1]. C3 glomerulopathy is characterized histopathologically by accumulation of the C3 component of complement in renal tissue. This finding, in the absence or near-absence of immunoglobulin deposits in a patient with the classic clinical features of glomerulonephritis, is the single diagnostic criterion.

Although the rarity of C3 glomerulopathy makes it difficult to derive precise incidence and prevalence figures, a number of small cohort studies have generated estimates, although these are of limited reliability. In the United States, the incidence of C3 glomerulopathy is estimated to be between ~1 case per 1,000,000 and ~2–3 cases per 1,000,000 based on an

analysis of C3 glomerulopathy registry data (49 cases per year over the past 3 years)[2]. The prevalence might be as low as 5 cases per 1,000,000 in the United States[3]. Data derived from four European studies provide estimates of ~0.2–1.0 cases per 1,000,000 of the population[4-6]. Point prevalence values range from 14 to 140 cases per 1,000,000 (Table 1).

The presentation of C3 glomerulopathy ranges from asymptomatic haematuria and proteinuria to an acute presentation with the classic signs and symptoms of glomerulonephritis. Patients often have a history of haematuria and hypertension, which can be severe, and might be an associated history of acute kidney injury (AKI) and/or chronic kidney disease (CKD). Serum C3 levels are low in the majority of patients and are often the first indication that C3 glomerulopathy should be included in the differential diagnosis[2,5]. The ultimate trigger for kidney biopsy is typically continued haematuria and/or proteinuria in the face of persistently low serum levels of C3.

Considerable knowledge gaps exist in our understanding of the natural history of C3 glomerulopathy, not only because of the rarity of the disease but also because nomenclature changes and the inclusion of dissimilar cases in historical cohorts obscure the data and preclude meaningful conclusions from being drawn. Nevertheless, the most important adverse outcome associated with the diagnosis of C3 glomerulopathy is progression to end-stage renal disease (ESRD), which occurs within 10 years of diagnosis in ~70% of affected children and 30–50% of affected adults[2,5,7]. Histological evidence of disease recurrence can be documented almost immediately after renal transplantation, and contributes to allograft loss in ~50% of patients within 10 years of transplantation[8-10].

This Review describes the state of the art with regard to current understanding of C3 glomerulopathy. We present insights relating to the histopathological diagnosis of C3 glomerulopathy and describe the crucial role of complement dysregulation in its pathogenesis. Genetic and acquired drivers of the disease, potential biomarkers, and available treatment options are also presented. All authors of this Review participated in the C3 Glomerulopathy Focus Group Meeting, which was held in Copenhagen on 8 September 2017 immediately before the 16th European Meeting on Complement Human Diseases 2017. Material included in this paper reflects in part the content of those presentations.

Renal pathology

C3 glomerulopathy is a histopathological diagnosis. The disease is defined by the presence in renal biopsy samples of a glomerulonephritis with sole (or at least dominant) glomerular immunofluorescence staining for C3 of at least two orders of magnitude greater intensity than for any other immune reactant[11]. The C3 deposits observed in immunofluorescence studies range from semi-linear to granular in texture. The panel of antibodies used for immunofluorescence studies in most renal pathology laboratories includes antisera to immunoglobulin heavy chains (IgG, IgM and IgA), immunoglobulin light chains (κ and λ) and the complement components C1q and C3. The antibody to C3 is specific for C3c, a stable C3 cleavage product.

Electron microscopy is necessary to distinguish the two major subtypes of C3 glomerulopathy, DDD and C3GN. In DDD, electron microscopy reveals highly electron-dense, osmiophilic deposits with a 'sausage-shaped' or 'Chinese calligraphy-like' appearance that thicken and transform the lamina densa of the glomerular basement membrane (GBM). Similar extremely electron-dense deposits can also be identified in Bowman's capsules and some tubular basement membranes. In C3GN, by comparison, the electron density of deposits approaches that of the glomerular matrix components. These deposits often have an amorphous cloudy appearance within the mesangium and can appear as ill-defined, subendothelial (intramembranous and/or subepithelial) inclusions. Subepithelial humps can occur in both subtypes.

Findings on light microscopy are diverse, and range from no glomerular hypercellularity to mesangial proliferative, endocapillary proliferative, exudative, membranoproliferative, crescentic and sclerosing patterns. The deposits often stain negative on Jones methenamine silver stain and red on Masson trichrome stain.

Laser microdissection and mass spectrometry studies identify large amounts of C3, most commonly C3dg (a cleavage product of C3) with limited amounts of C5, C6, C7, C8 and C9, as well as of the five complement factor H-related proteins (FHR1–FHR5). The presence of terminal complement complements is more typical of C3GN than DDD[12,13] (Figure 1). Notwithstanding this new approach to its classification, however, C3 glomerulopathy is not a newly recognized disease[14]. DDD has been known for decades as membranoproliferative glomerulonephritis (MPGN) type 2, and C3GN was historically classified as atypical MPGN type 1 and type 3[11].

Challenges in diagnosis

A number of challenges hinder the diagnosis of C3 glomerulopathy. In particular, subjectivity influences the grading of immunofluorescence staining intensity. The requirement for a difference of at least two orders of magnitude between the staining intensity of C3 and that of any other immunoreactants derives from a systematic analysis of immunofluorescence findings in a large well-defined cohort of patients with biopsy-confirmed C3 glomerulopathy[15]. In that study, staining intensity in frozen tissue was graded on a scale of 0, trace, 1+, 2+ and 3+, using DDD as the prototypic C3 glomerulopathy. Application of the strictest definition (C3-only staining) captured only ~50% of DDD cases. A slightly broader definition (C3-dominant with up to 1+ IgM) increased case recovery to 71.4%. Further broadening of the diagnostic criteria (C3 dominant by at least 2 orders of magnitude) identified 88.1% of DDD cases. Finally, the broadest criteria (C3 dominant by at least 1 order of magnitude) identified a further 4.8% of DDD cases but at the cost of reduced specificity. On the basis of these findings in DDD,, C3 dominance of at least 2 orders of magnitude was adopted as the optimal defining immunofluorescence criteria for all C3 glomerulopathy[1,15]. Application of these criteria to biopsy samples from patients with other forms of MPGN led to reclassification of 30.5% of patients with MPGN type 1 and 39% of patients with MPGN type 3 as having C3 glomerulopathy[15].

Immune complex glomerulonephritis

Classification has been further complicated by the observation that diagnosis as either immune complex glomerulonephritis (ICGN) or C3GN seems to depend on the immunostaining technique and tissue preparation methods used (namely, frozen tissue versus formalin-fixed, paraffin-embedded tissue). The performance of immunofluoresence on frozen tissue and immunoperoxidase on formalin-fixed, paraffin-embedded tissue has been compared in small numbers of biopsy samples. The researchers concluded that immunofluorescence on frozen tissue is more sensitive and more reliable than immunoperoxidase on formalin-fixed, paraffin-embedded tissue for grading C3 staining intensity[16]. Moreover, the transport media used can mask any immunoglobulins present, thereby preventing their detection by routine tests and altering their apparent staining intensity relative to that of C3 on standard immunofluorescence[8]. Pronase immunofluorescence is helpful in these circumstances, as the unmasking of immunoglobulins might be sufficient to change the diagnosis from C3GN to ICGN. Demonstration of negative glomerular staining for C4d can also be helpful to exclude ICGN and to rule out masked immunoglobulin deposits[17].

Post-infectious glomerulonephritis

Co-deposition of IgG and C3 is commonly observed in patients with post-infectious glomerulonephritis (PIGN), and C3-dominant glomerular deposition might represent a late stage of this disease. The 2013 consensus meeting acknowledged the similarity of PIGN and C3 glomerulopathy and the difficulty of distinguishing between these two diseases on the basis of pathological features alone[1,17]. The consensus recommendation therefore was to label this disease as C3-dominant PIGN (Figure 1). The patient's clinical course and laboratory findings ultimately differentiate between these diseases and determine the need for treatment, as nearly all patients with PIGN regain their baseline kidney function and experience resolution of haematuria, proteinuria and hypocomplementaemia within a few weeks without requiring therapeutic intervention.

In patients with presumed PIGN, if abnormalities including the presence of hypocomplementaemia, progressive decline in kidney function, and/or notable proteinuria (>500 mg daily) persist for >12 weeks, a biopsy should be performed[18]. If the biopsy findings are consistent with C3 glomerulopathy, the diagnosis might be changed to C3 glomerulopathy and investigation of the complement cascade is indicated. Although the currently accepted (biopsy-based) definition of C3 glomerulopathy identifies the majority of patients with PIGN who have an underlying complement dysregulation, some degree of diagnostic fluidity has been noted in patients in whom repeat biopsies were obtained (for example, although the initial biopsy sample might indicate C3 glomerulopathy, a biopsy sample taken later in the disease course might reveal ICGN, and vice versa)[15]. Of note, some data suggest that complement dysregulation might also underlie ICGN in a few patients[8].

Predictors of progression

The continued and unchecked complement activity characteristic of C3 glomerulopathy incites glomerular inflammation and subsequent scarring, which leads to chronic and irreversible kidney damage. In one study, a histological index of disease activity and

chronicity was applied to a large North American cohort of patients with C3 glomerulopathy (87 with C3GN and 24 with DDD)[3]. The following features were scored: mesangial hypercellularity, endocapillary proliferation, membranoproliferative morphology, glomerular leukocyte infiltration, cellular and fibrocellular crescents, fibrinoid necrosis and interstitial inflammation (each on a scale of 0–3). The features graded for the chronicity score included glomerulosclerosis (segmental and global), the percent cortical area with tubular atrophy, the percent cortical area with interstitial fibrosis (each on a scale of 0–3), and arteriosclerosis (on a scale of 0–1)[19].

The total disease activity and total chronicity scores were both strong independent predictors of progression of C3 glomerulopathy, although the chronicity index was the more powerful predictor of outcome. In multivariable models that assessed the contribution of individual clinical and pathological features, the estimated glomerular filtration rate (GFR) at diagnosis, percent tubular atrophy and percent cortical area with interstitial fibrosis emerged as the strongest independent predictors of progression to loss of kidney function. Whether histological disease activity and chronicity scores will suffice to indicate the potential to respond to treatment remains to be seen. However, an assessment of histologic disease activity and chronicity should be considered in patient care as these findings may inform management and prognosis[3].

The complement system

An understanding of the complement system (which is composed of >50 individual proteins or activation fragments, many of which can be either surface-bound or soluble) is required to provide context for the complexity of C3 glomerulopathy. The complement system is essential to both innate and adaptive immunity: a delicate balance between activating and regulatory mechanisms enables this system to target infectious microbes for destruction, clear immune complexes and apoptotic cells from the circulation, and augment the humoral response, while recognizing and leaving healthy cells undamaged (Figure 2).

Complement can be activated through the classical, lectin and alternative pathways, each of which has a unique trigger. Activation of the classical pathway involves the recognition of antigen–antibody complexes, whereas the lectin pathway is triggered by microbial polysaccharides. The alternative pathway is constitutively active, owing to the spontaneous hydrolysis of a reactive thioester on C3, a process known as tick-over. Once activated, these pathways lead to the formation of two C3 convertases, C4b2a via the classical and lectin pathways, and C3bBb via the alternative pathway. These C3 convertases cleave accessible C3 into C3a and C3b, enabling C3b to act as a foundation for docking of factor B, which is cleaved by factor D to generate additional C3bBb. This feedback mechanism provides robust amplification of the initial complement response, and as more C3bBb forms, the terminal pathway is activated by the generation of C3bBbC3b (and small amounts of C4b2aC3b, the C5 convertase of the classical and lectin pathways). These C5 convertases cleave C5 into C5a (a potent anaphylatoxin) and C5b (which initiates the terminal pathway), culminating in the generation of either soluble C5b-9 or the membrane attack complex (MAC), which induces cell lysis.

C3 is an acute phase reactant. It is produced in large quantities by the liver and has a daily turnover of ~40%. As one of the most abundant plasma proteins, C3 circulates at concentrations of ~1.2 mg/ml, ensuring its immediate availability to respond to stimuli such as the presence of infectious microbes. Factor B is also abundant in plasma, with a circulating concentration of ~0.2 mg/ml, and yet C3 and factor B do not spontaneously react. This equipoise reflects the existence of precise complement control mechanisms[20].

C3bBb, once formed, is so quickly degraded that its half-life is only ~90 s[21]. A number of regulators of complement activation (RCAs) tightly control this process. The most abundant RCA is factor H, which controls complement in both the fluid phase and on cell surfaces. The factor H-related family of proteins (FHRs) share a common structural motif based on functional units of ~60 amino acids called complement control protein domains or short consensus repeats (SCRs). Factor H has 20 SCRs and regulates complement by several mechanisms: by accelerating the decay of C3bBb; by providing a platform for the proteolytic inactivation of C3b to iC3b through its cofactor activity with factor I; and by inhibiting the conversion of C3bB to C3bBb, thereby preventing C3 convertase assembly[22-24]. The inhibitory actions of factor H and its alternatively spliced variant, factor H-like protein 1 (FHL1), depend on the ability of the first four SCRs of either protein to dock with C3b.

FHR1–FHR5 also include several structurally related SCR domains. Although they lack the complement-regulatory N-terminal SCRs found in both factor H and FHL1, several FHR proteins have C-terminal SCRs that are very similar to those of factor H. FHR1, for example, contains 5 SCRs, among which SCRs 4 and 5 are almost identical (with the exception of two amino acids) to SCRs 19 and 20 of factor H[25]. The structural similarity and sequence homology of these domains suggests that they have related functions. Although the precise role of FHR1 and other FHR proteins in regulation of complement remains to be determined, FHR1, FHR2 and FHR5 are thought to be competitive inhibitors of factor H-mediated regulation of complement, and FHR5 is thought to be a competitive activator of complement that interacts with properdin[26-29].

Pathogenesis of C3 glomerulopathy

Dysregulation of the alternative complement pathway in the fluid phase underlies C3 glomerulopathy. This relationship was originally demonstrated in a pig model of DDD,[30] after which more-sophisticated mouse studies provided additional important insights into our understanding of the disease process[31-35]. In mice with targeted deletion of complement factor H (*Cfh*$^{-/-}$ mice), for example, serum C3 is consumed and renal injury spontaneously develops. These mice develop renal pathology similar to human C3 glomerulopathy, including C3 glomerular deposition in the absence of immunoglobulin and subendothelial electron-dense deposits that resemble C3GN[31]. Introducing a second genetic change, deletion of properdin (*Cfh*$^{-/-}$*Cfp*$^{-/-}$ mice) favours dysregulated activity of C3 convertase over C5 convertase activity and subtly alters the histopathological phenotype from C3GN-like to DDD-like[32,33]. If factor B is deleted instead of properdin (*Cfh*$^{-/-}$*Cfb*$^{-/-}$ mice), C3bBb C3 convertase cannot form and the renal phenotype is prevented[31]. However if C5 is absent instead (*Cfh*$^{-/-}$*C5*$^{-/-}$ mice), C3 glomerulopathy is not prevented even though the

terminal pathway is absent, although disease severity is markedly decreased[34]. In aggregate, these genetic manipulations have been very valuable in confirming that uncontrolled activation of the alternative pathway drives the pathogenesis of C3 glomerulopathy (Table 2). These studies also support the development of methods of blocking C3 convertase formation as a strategic approach to the treatment of this disease.

Complement control in the glomerulus

The effects of complement dysregulation in C3 glomerulopathy are manifested in the glomerular microenvironment. During ultrafiltration, water and solutes reach the Bowman's space by passing through the glomerular filtration barrier, which consists of the glycocalyx, endothelial fenestrae, GBM and slit diaphragm[37]. The first barrier, the glycocalyx, is a carbohydrate-rich layer anchored to the cell membrane by proteoglycans, which, along with glycosaminoglycans, provide the glycocalyx with its structural stability and barrier function. The major glycosaminoglycans include unsulfated hyaluronan, sulfated heparan and chondroitin sulfates. The most abundant glycosaminoglycan is hyaluronan, which imparts to the glycocalyx its gel-like texture, whereas heparan sulfate contributes to the specific binding of numerous ligands owing to its enormous structural diversity. In aggregate, the glycocalyx is composed of over 150 proteins, mostly extracellular matrix components. This complexity suggests that many glycocalyx components contribute to the development of glomerular disease[38].

The glomerular glycocalyx undergoes continuous turnover, although the glycocalyx filling the endothelial pores (fenestrae) is relatively stable[39]. Complement control in this microenvironment is essential and occurs in a complicated and multifaceted way[40]. Glomerular endothelial cells express MAC inhibitory protein (also known as CD59) and membrane cofactor protein (also known as CD46). CD59 is attached to glomerular endothelial cells by a glycophosphatidylinositol anchor and inhibits the terminal complement pathway by preventing C9 polymerization and MAC formation. CD46 provides control of proximal complement pathways. This transmembrane protein belongs to the RCA protein family and acts as a cofactor for factor I-mediated cleavage of C3b and C4b to prevent C3 convertase formation[41].

Complement control within the glomerular endothelial pores is largely modulated by factor H and FHR proteins[28,42-44]. In healthy individuals, FHR1, FHR2 and FHR5 dimerize through their two N-terminal SCR domains to form a repertoire of homodimeric and heterodimeric complexes. When, as a consequence of genetic rearrangement, these dimerization domains are duplicated, abnormal FHR protein complexes can form, the functional consequence of which is complement dysregulation (Figure 2, Table 3)[45-48]. As described in the next section, these rearrangements are an important genetic cause of C3 glomerulopathy. FHR5, additionally, binds to the extracellular matrix and enhances complement activation via competitive inhibition of factor H binding[49].

The importance of tight complement control in the glomerular microenvironment is supported by the evidence of some degree of C3 immunoreactivity in the glomeruli of ~33% of kidneys from clinically normal donors and at autopsy[50,51]. C3 deposition along the GBM reflects an affinity of this complement component for specific glycocalyx proteins,

consistent with the finding that C3 preferentially binds to laminin rather than to type IV collagen and fibronectin[52]. In aggregate, these data point to unique features of complement regulation specifically in the glomerulus, and suggest that studies focused on the complement–glycocalyx relationship would provide important insights into our understanding of C3 glomerulopathy.

Genetic factors

Comprehensive genetic testing has demonstrated that ~25% of patients with C3 glomerulopathy carry rare or unique variants in complement-related genes[5,8,53-55]. These variants are usually found in the two convertase genes — *C3*, which encodes complement factor 3, and *CFB*, which encodes complement factor B (complexes of these two proteins form C3bBb (C3 convertase) and C3bBbC3b (C5 convertase)); in the complement regulator genes *CFH* and *CFI*, which encode complement factors H and I, respectively; or in *CFHR5*, which encodes complement factor H-related protein 5 (an enhancer of complement activation)[53]. Gene-specific 'hot spots' for rare variants have also been identified. In *CFH*, for example, rare missense variants are clustered in the sequence encoding the N-terminal portion of the protein that contains the C3b binding site (which is important for fluid-phase complement control) and are not found in the sequence encoding the cell-surface heparin-binding site[55]. This distribution pattern recapitulates the pathophysiology of C3 glomerulopathy, which involves dysregulation of the alternative pathway in the circulation as opposed to on the cell surface[55]. It is also not unusual for patients with C3 glomerulopathy to carry multiple variants in complement-related genes. Such genetic complexity might partially explain why families in which the affected individual has a first-degree or second-degree relative with the same diagnosis are very rare. Specific haplotypes can contribute to the variable penetrance of C3 glomerulopathy by increasing or decreasing the likelihood of disease, possibly by affecting circulating levels of specific complement proteins[5,8,55].

Among patients who are identified as having familial C3 glomerulopathy, the renal phenotype is more commonly C3GN than DDD. The most frequent genetic finding in these patients is rearrangement of the *CFH* locus, which creates novel *CFHR* fusion genes. These genes are transcribed and translated into new FHR fusion proteins, such as FHR1–FHR1, FHR3–FHR1, FHR2–FHR5, FHR5–FHR5 and FHR5–FHR2[4,35,36,45-48]. A feature shared by all these fusion proteins is the addition of two N-terminal SCR domains, which generates an extra dimerization domain that enables these fusion proteins to form novel FHR complexes (Table 3). These complexes bind to the glyocalyx and act as competitive inhibitors of factor H, thereby altering complement control in this microenvironment[26,28,49].

The most commonly reported genomic rearrangement in the *CFH* region is a *CFHR5* gene variant, endemic in Cyprus, that creates an FHR5–FHR5 fusion protein in which the first two SCRs of FHR5 are duplicated (Table 3)[46]. The phenotypic consequence of this abnormal FHR5 protein is variably penetrant C3GN. Among carriers of this *CFHR5* gene variant, 90% have microscopic haematuria; 40% also develop proteinuria, which portends progression to CKD in nearly all patients. The duration of disease is an important contributor to the development of ESRD, and ~80% of affected men and 20% of affected women over 50 years of age progress to ESRD. The reason for the increased severity of

disease in men is unclear[6]. The remaining fusion proteins illustrated in Table 3 have been identified in small families that have attracted research interest owing to the diagnosis of C3 glomerulopathy (usually C3GN) in several family members.

Acquired factors

In patients with C3 glomerulopathy, complement dysregulation is frequently driven by autoantibodies to a variety of complement proteins and complexes (Figure 2). Identifying and measuring the levels of these autoantibodies provides insight into the underlying pathophysiology of complement dysregulation and offers a biomarker for monitoring the course of disease (Table 4). Because the identification of these autoantibodies is not trivial, specialized laboratories are required to conduct these studies.

The most frequently identified autoantibodies target C3bBb. Known as C3 nephritic factors, these autoantibodies stabilize C3 convertase and increase its half-life, which leads to increased consumption of C3 in serum. C3 nephritic factors are reported in up to ~80% of patients with DDD and ~50% of those with C3GN, although there are broad inter-individual differences in the nature and/or the level of C3 nephritic factors[63]. C5 nephritic factors (autoantibodies that target C3bBbC3b) are also common[57]. They are more frequently detected in patients with C3GN than in those with DDD, and can be associated with high serum levels of soluble C5b-9. Less frequently detected are C4 nephritic factors (autoantibodies to C4b2a), factor H autoantibodies and factor B autoantibodies, which collectively are found in about 10% of patients with C3 glomerulopathy[58,59]. Some patients are positive for multiple autoantibodies[56,63-66].

The relationship between C3 nephritic factors and disease outcome has been studied in 40 patients (13 children, 27 adults) who had severe C3 glomerulopathy at onset, defined as AKI and/or nephrotic proteinuria and/or proliferative glomerulonephritis. All patients were positive for C3 nephritic factors. Patients were divided into two groups on the basis of GFR decline: 21 patients with rapid progression (defined as a GFR decline ≥5ml/min per year) and 19 patients with slow progression (defined as a GFR decline <5ml/min per year). The two groups did not differ in terms of age at disease onset, proteinuria and renal function; however, median renal survival was 30 months in the patients with rapid progression versus 288 months in the patients with slow progression. Although the frequency of other autoantibodies (including C5 nephritic factors, anti-factor H, anti-C3b and anti-factor B antibodies) was similar in the two groups, the capacity of the patients' IgG to stabilize C3 convertase was significantly higher in the rapid progression group than in the slow progression group ($P = 0.04$)[67]. Whether identifying and neutralizing or removing these antibodies will offer a treatment advantage remains to be determined; however, given the success of such treatment in other autoantibody-associated glomerular diseases, it seems reasonable to consider C3 nephritic factors (and other autoantibodies) as potential treatment targets.

Patients with C3 glomerulopathy aged >50 years (see next section) should be evaluated for the presence of a monoclonal gammopathy. The clinical presentation associated with monoclonal proteins is broad, and — in addition to the classic malignancies, such as

multiple myeloma and Waldenström macroglobulinaemia — includes nonmalignant disorders related to clonal paraproteins, such as light-chain amyloidosis and incidentally detected premalignant plasma cell dyscrasias. These conditions are generally termed monoclonal gammopathy of undetermined significance (MGUS), but when the monoclonal gammopathy is associated with renal disease, the term monoclonal gammopathy of renal significance (MGRS) is used. Although it can be difficult to prove a causal relationship between the paraprotein and complement dysregulation in C3 glomerulopathy-related MGRS, in a few patients who have been extensively studied, the monoclonal protein has been demonstrated to interact with complement regulatory proteins[58,60,66]. For example, the first such report described a 57-year-old woman with alternative pathway dysfunction secondary to a 46 kD monoclonal immunoglobulin λ light chain dimer that activated the alternative pathway in a dose-dependent and ionic-strength-dependent manner. The light chain dimer interacted directly with factor H and compromised its ability to control C3 convertase activity[66]. These findings have clear therapeutic implications, as monoclonal gammopathy-targeted treatment could result in remission and stabilization of kidney function in a subset of these patients[60].

Management of C3 glomerulopathy

Presentation and evaluation

Patients with C3 glomerulopathy typically present with proteinuria and haematuria. Although all age-groups are affected, their disease triggers differ. For example, in children and young adults, C3 glomerulopathy is often preceded by an upper respiratory tract infection[68,69]. A careful review of the history in these patients might also reveal exacerbations of proteinuria and haematuria during episodes of reinfection[69]. Mean age at diagnosis is lower for patients with DDD than for those with C3GN.[70,71] DDD is also less common, being diagnosed approximately half as frequently as C3GN[70]. The extreme rarity of both diseases hampers the collection of precise epidemiological data, and since the sole diagnostic criterion requires interpretation of a renal biopsy sample, incidence and prevalence estimates are affected by regional biopsy and referral practices. As many older patients who present with C3 glomerulopathy will have a detectable paraprotein in the serum or urine, indicative of MGRS[68], the inclusion of patients with MGRS in these statistics increases the mean age at diagnosis of C3GN and its prevalence (relative to DDD) by 5–10 cases of C3GN for each case of DDD[60-62,68].

All patients aged ≥50 years should be screened for paraproteins by serum protein electrophoresis immunofixation and serum free light chain evaluation. Although a precise age threshold for such screening has not been defined, in the most extensive clinical review of C3 glomerulopathy to date, monoclonal gammopathy was identified in only 8 of 52 (15%) patients younger than 50 years of age, compared with 28 of 43 (65%) patients above this age[68]. A diagnosis of monoclonal gammopathy mandates further evaluation with a bone marrow biopsy to identify the clonal population responsible for production of the monoclonal antibody. Routine complement studies might also help to define how the monoclonal immunoglobulin affects complement regulation. However, in many of these

patients, complex investigations are required that are often only available in specialist laboratories or in research settings[60-62,68] (Figure 3).

Expert opinion recommends that all patients with C3 glomerulopathy should undergo a comprehensive complement evaluation that includes assessment of overall complement activity, measurements of serum levels of complement proteins and their split products, and screening for autoantibodies[72]. In the context of this evaluation, low serum C3 levels, high serum levels of soluble C5b-9 and high stabilizing capacity of C3 nephritic factors have been identified as biomarkers predictive of aggressive complement dysregulation and rapid progression to ESRD[67]. Noteworthy but subtle differences in complement biomarkers between DDD and C3GN (for example, in levels of C5, properdin and soluble C5b-9) reflect underlying differences in the degree of convertase dysregulation[1,2,57,63]. In DDD, for example, dysregulation of C3 convertase is typically greater than dysregulation of C5 convertase, whereas in C3GN the reverse pattern is seen[57,63]. This distinction might influence treatment decisions once new anti-complement therapies become available.

Genetic testing should be considered, and should include screening of *C3, CFB, CFH, CFHR5* and *CFI*, as well as testing for copy number variations and rearrangements of the *CFH–CFHR* gene cluster. Identifying these rearrangements is challenging and typically available only in specialized laboratories. Although the precise value of genetic testing remains to be defined in the clinical setting, patients with C3 glomerulopathy who carry mutations in complement genes seem to respond more poorly to mycophenolate mofetil than do those who are positive for nephritic factors[7,68]. Further studies will be required to verify this possible association.

All patients with C3 glomerulopathy should undergo screening for autoantibodies. C3 nephritic factors and C5 nephritic factors are the autoantibodies most frequently identified (Figure 2, Table 4). The capacity of C3 nephritic factors to stabilize convertase activity should also be evaluated, as highly stabilizing activity is associated with rapid progression of disease[67]. Other autoantibodies (such as C4 nephritic factors, factor H autoantibodies and factor B autoantibodies) are far less common but should still be screened for, especially in patients with C3 glomerulopathy-related monoclonal gammopathy[56,60,68]. Whether the types or properties of these autoantibodies change over time, or whether epitope spreading occurs, is not yet known. It is also unknown whether therapies targeting these antibodies might offer a treatment advantage.

Treatment

An optimal treatment for C3 glomerulopathy has not been established (Figure 3). Appropriate measures that support general good health should be offered, alongside angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers as first-line therapy for proteinuria and blood pressure control. This approach was associated with substantially improved renal survival in a retrospective study conducted in French patients with C3 glomerulopathy[5]. Lipid-lowering agents should also be considered[73,74].

Plasma therapy and exchange.

Robust data supporting the use of plasma therapy in patients with C3 glomerulopathy are lacking; however, occasional case reports describe favourable outcomes for such therapy when a mutated protein has been identified and is causally implicated in the disease. For example, plasma therapy was effective in a pair of siblings with C3 glomerulopathy caused by homozygosity for an in-frame amino-acid deletion in factor H that altered its ability to control complement activity[75]. Plasma therapy has also been useful in patients with C3 glomerulopathy who have AKI, but has been unsuccessful in patients with C3 nephritic factors, presumably because production of these autoantibodies continues after they are removed. One 15-year-old girl with recurrence of DDD after renal transplantation received thrice-weekly plasma exchanges, which were successful in removing circulating C3 nephritic factors; however, when this treatment was discontinued (after more than 100 exchanges) the allograft failed[76]. These data suggest that the precise role for plasma therapy in C3 glomerulopathy patients remains to be defined.

General immunosuppressive therapy.

Although immunosuppressive therapy has the potential to inhibit the cellular immune response associated with C3 glomerulopathy by decreasing autoantibody production and limiting the anaphylatoxic effects of C3a and C5a, the effectiveness of this approach has been mixed. In a study that included 21 patients with DDD and 59 patients with C3GN[4], both groups had a 10-year renal survival <50%, and 29% of patients progressed to ESRD after only 28 months. Although 32 patients received immunosuppressive treatment, either with corticosteroids alone (22 patients) or with corticosteroids plus other drugs (10 patients), univariate and multivariate analysis showed that these treatments failed to reduce progression to ESRD.

A separate study included 29 patients with DDD, 56 patients with C3GN, and 49 patients with ICGN (MPGN type 1)[5]. Across the entire cohort, 10-year renal survival was 63%, with no differences between groups. When the analysis was restricted to adult patients, however, those with DDD had the worst prognosis. Immunosuppression did not alter renal survival.

By contrast, immunosuppression was helpful in altering the disease course in Spanish patients with C3 glomerulopathy[7]. This study included 60 patients (median follow-up 47 months) divided into three groups: 22 received mycophenolate mofetil plus corticosteroids; 18 received other immunosuppressive treatments (including 11 who received corticosteroids alone and 7 who received corticosteroids and cyclophosphamide); and a control group of 20 patients did not receive any immunosuppression. Dosage and duration of immunosuppressive therapy were based on physician preference. The median initial dose of mycophenolate mofetil was 1 g (range 0.75–2.00 g) daily and the mean duration of treatment was 18 months (range 10–49 months). Progression to ESRD differed greatly between the groups: 0 and 3 patients in the mycophenolate mofetil and other immunosuppression groups, respectively, went on to require dialysis, compared with 7 patients in the control group. Doubling of serum creatinine levels (a secondary outcome measure) occurred in 14 patients, 7 in the other immunosuppression group and 7 in the control group. Rates of remission were significantly higher in the mycophenolate mofetil

group than in the other immunosuppression group (19 of 22 patients versus 9 of 18 patients; $P < 0.05$).

A relative limitation of this study was that genetic and complement data were available for only 23 of 60 patients. Within the subgroup of 11 patients who were positive for C3 nephritic factors, 8 of the 10 patients who received immunotherapy went into remission, and the other 2 patients progressed to ESRD. By contrast, within the subgroup of 12 patients without C3 nephritic factors, only 3 of the 8 patients who received immunotherapy went into remission; the remaining 5 patients progressed to ESRD. Genetic testing identified mutations in only three patients: a heterozygous missense mutation in *C3*, a heterozygous missense mutation in *CFH* and a risk polymorphism in *CD46*. These three patients all developed ESRD despite immunotherapy.

In a subsequent study, 30 patients with C3 glomerulopathy received 6 months of a tapering alternate-day steroid regimen together with 1 year of mycophenolate mofetil therapy[77]. At follow up (mean almost 3 years), two-thirds of the patients had responded to this treatment, defined as stabilized or reduced serum creatinine levels and reduced proteinuria. Baseline levels of serum creatinine and proteinuria were not significantly different between the groups of responders and non-responders, although responders had higher baseline levels of soluble C5b-9. When this cohort was compared to a different group of 42 patients with C3 glomerulopathy treated with corticosteroids alone or a variety of other immunomodulatory medications, they had a superior outcome[77].

By contrast, treatment with mycophenolate mofetil had no beneficial effect in a cohort of 24 patients[68]. Responses varied widely, and at follow-up (median duration of therapy 9.6 months), 1 patient had a complete response, 2 patients showed a partial response, 4 patients had stable disease and 15 patients (3 of whom progressed to ESRD) showed no response[68]. Nevertheless, the researchers concluded that renal outcome was improved in patients managed with immunosuppression compared with those managed conservatively. It is perhaps noteworthy that this study included fewer patients who were positive for C3 nephritic factors and more patients identified as mutation-positive[68] than the Spanish study discussed above[7], which might account for the difference in rates of response to mycophenolate mofetil between these two studies.

In summary, the data from these studies are difficult to reconcile, and which patients are most likely to respond to mycophenolate mofetil therapy remains unclear. A well-designed prospective trial with comprehensive genetic testing and complement data will be required to determine whether a particular subgroup of patients with C3 glomerulopathy truly benefits from this treatment approach. Additionally, when C3 glomerulopathy is associated with monoclonal gammopathy, treatment with chemotherapy or other immunosuppressive treatment is warranted to achieve a haematologic response. In this specific setting, therapy directed toward the B-cell clone might result in improved renal survival[60-62].

Anti-complement therapy with eculizumab.

The central role of complement dysregulation in the pathogenesis of C3 glomerulopathy has focused attention on anti-complement agents as potential treatments. Several case reports

and a few case series support the use of anti-C5 therapy with eculizumab in a subset of patients with C3 glomerulopathy (reviewed elsewhere[78]). The single trial conducted to date was an open-label, proof-of-concept, efficacy and safety study that involved three patients with DDD (including one renal transplant recipient) and three patients with C3GN (including two renal transplant recipients), all of whom had proteinuria >1 g daily and/or AKI at enrollment.[79] Genetic and complement testing identified pathogenic variants in *CFH* and *CD46* in one patient each and C3 nephritic factors in three patients. After 12 months of twice weekly eculizumab therapy, one patient with DDD and one with C3GN showed considerably reduced serum creatinine levels, one patient with DDD had a marked reduction in proteinuria, and one patient with C3GN and stable laboratory parameters had histopathologic evidence of improvement. In all patients who had elevated levels of soluble C5b-9 at baseline, the treatment normalized this biomarker of terminal pathway activity. The authors concluded that some but not all patients respond to eculizumab, and that an elevated soluble C5b-9 level is a potentially useful marker of response to this agent.

The results of a recent retrospective study from France has provided a more nuanced picture of the use of eculizumab in 26 patients (including 13 children or adolescents) with C3 glomerulopathy who were treated for a median duration of 14 months[80]. The indications for eculizumab were CKD (11 patients), rapidly progressive disease (7 patients) and dialysis (3 patients). On eculizumab, 6 patients (23%) had a global clinical response, 6 (23%) had a partial clinical response, and 14 (54%) had no response. As compared to those with a partial clinical response or no response, the patients with a global clinical response had lower estimated GFRs, more rapidly progressive disease, and more extracapillary proliferation in kidney biopsy samples. Age, extent of renal fibrosis, frequency of nephrotic syndrome, and the proportion of patients with features of alternative pathway activation did not differ across the three groups. These results are consistent with the fact that eculizumab mainly targets a single aspect of C3 glomerulopathy — namely, glomerular inflammation — and has no effect, or only a limited effect, on the C3 complement dysregulation that is the main driver of the disease (Figure 2). This finding mirrors data generated in animal models of C3 glomerulopathy, which show that C5 blockade alleviates glomerular inflammation and reduces proteinuria but does not affect complement deposition in the kidney (Table 2).

New anti-complement therapies.

Clinical trials investigating a variety of anti-complement drugs are underway or on the horizon (Table 5). Recruitment of patients is ongoing for four randomized, double-blind, placebo-controlled phase II studies to test avacopan, an oral C5aR1 inhibitor[81]; ACH0144471, an oral factor D inhibitor[82,83]; OMS721, an intravenously administered anti-MASP2 monoclonal antibody[84]; and APL2, a subcutaneously administered pegylated C3 inhibitor[85]. Clinical trials are expected to begin soon for two other drugs: AMY101, a subcutaneously administered C3 inhibitor, and LPN023, an oral factor B inhibitor (see Table 5 for drugs and Figure 2 for their targets). This progress suggests that new therapies could soon emerge for C3 glomerulopathy; however, given the complexity of the underlying disease, it is possible that no single treatment will be universally appropriate. This prospect mandates comprehensive evaluations of complement function and genotype for each patient

included in every trial, to enable responses to be matched with the type of intervention (Figure 2).

Transplantation.

Data on transplantation outcomes are sparse. Although C3 glomerulopathy was not recognized prior to 2013, some information can be derived from a study of allograft failure in 189,211 primary kidney transplant recipients included in the United Network for Organ Sharing (UNOS) database from September 1987 to May 2007[9], because this study included some patients with MPGN type 2 (an alternative designation for DDD). Noteworthy findings in these patients are the rarity of this diagnosis (0.03% in the US ESRD population), the long interval from diagnosis to ESRD (average ~10 years), and the poor allograft survival rate. Age at transplantation seemed to have a large effect on graft survival, with 10-year survival experienced by only 8 of 72 (11%) paediatric allograft recipients, in contrast to 22 of 107 (20.6%) adult recipients. This difference might reflect more-aggressive disease in the paediatric population, a hypothesis supported by some studies but refuted by others[69,86], or simply that these data are not sufficiently complete to identify factors predictive of outcome in allograft recipients with DDD.

The largest available study of transplantation outcomes in patients with C3GN included 21 patients[10]. Median age at the time of initial diagnosis (which was based on biopsy findings in the native kidney) was 20.8 years and the median time to ESRD was just over 3.5 years, consistent with a slow but progressive decline in renal function. Most patients opted for renal replacement therapy prior to transplantation and so the median age at transplantation was 36 years. Recurrence of C3GN occurred in 14 patients (67%), usually within 2–3 years of transplantation. In 10 patients, recurrence was suspected on clinical grounds (the presence of haematuria, proteinuria or elevated serum creatinine levels) and confirmed by analysis of biopsy samples obtained to evaluate these symptoms; however, in four patients (29%), recurrent C3GN was identified in protocol biopsy samples, which were obtained in all patients at 0, 4, 12, 24, 60 and 120 months. In these four patients, the biopsy samples showed C3 deposition and other features of C3GN prior to the development of clinical symptoms.

Once recurrence of C3GN was confirmed by biopsy findings, the median time to graft failure was only 18 months. Intergroup comparisons were remarkable in three ways: first, the group without C3GN recurrence included six men and one woman, whereas the group with recurrence included six men and eight women, although these numbers are too small to determine whether the likelihood of recurrence is genuinely higher in women ($P = 0.06$). Second, the *HLA-DR17(3)-DQ2* haplotype (which is associated with other autoimmune disorders, such as type 1 diabetes mellitus) was carried by 6 of 14 (43%) patients with recurrence of C3GN versus only 1 of 7 (14%) patients without recurrence. Importantly, however, ~25% of white European populations have this haplotype[87]. Finally, although pre-transplantation serum C3 levels were available for only some of the 21 patients, none of five recurrence-free patients had low pretransplantation C3 levels, whereas six of eight patients with recurrent C3GN had very low pre-transplantation C3 levels (median 1.65 μmol/l; normal range 3.75–8.75 μmol/l). Although an isolated measurement of a low C3 serum level

does not permit definitive conclusions to be drawn about complement dysregulation, these results are consistent with ongoing complement activity in the majority of patients with recurrent C3GN who had some complement testing.

In aggregate, the available data point to a high risk of recurrence of C3 glomerulopathy in renal allografts for both DDD and C3GN patients. However, prediction of transplantation outcomes seems to be nuanced and complex. Important potential predictive factors include sex, age, genotype, autoantibodies and the current status of complement dysregulation. Although no specific data are available to guide decisions surrounding transplantation, and current recommendations are based on expert opinion and case reports[9,10,72], these observations support the value of genetic studies and complement evaluations prior to transplantation. The results of these investigations can not only inform pre-transplant decisions (that is, whether to perform a transplant in a patient with obvious complement dysregulation or clear genetic disease-causing mutations) but also post-transplantation treatment options, such as whether to consider complement blockade if terminal pathway dysregulation develops and C3 deposition is documented in an allograft biopsy.

Conclusions

C3 glomerulopathy is a rare and complex renal disease driven by complement dysregulation. The typical patient presents with classic signs and symptoms of glomerulonephritis, namely proteinuria, haematuria and hypertension, in association with low C3 levels, which reflect a complement abnormality. Renal biopsy is required to establish the diagnosis and must show glomerular C3 staining of at least two orders of magnitude greater intensity than for any other immunoreactant. Electron microscopy findings can differentiate the two subtypes of C3 glomerulopathy, DDD and C3GN. In both forms of the disease, uncontrolled complement activity leads to progressive glomerular inflammation and scarring with eventual chronic and irreversible damage that portends ESRD even if complement regulation is restored.

Clinical evaluation, which should include genetic testing, assays of complement function, measurement of complement protein levels and screening for autoantibodies, will identify complement dysregulation in most patients. Collaboration between the clinician, renal pathologist and biochemical or genetic laboratory is required to elucidate both the underlying pathogenesis and the optimal therapeutic approach[88]. A critical need remains for studies of the natural history of C3 glomerulopathy to enable the integration of clinical data with findings from pathology, genetic and complement biomarker studies.

An optimal treatment for C3 glomerulopathy has not yet been established. However, some patients with C3 glomerulopathy seem to respond to mycophenolate mofetil and/or eculizumab. For the majority of patients, however, new therapies will be required. Clinical trials to test new therapeutic agents are challenging to perform and their results are heavily influenced by the paucity of patients and the heterogeneity of disease. As such, the scientific and health-care communities have an obligation to educate patients and families about their disease and the pros and cons of the different clinical trials. In clinical trials, researchers

must ensure that each patient is maximally evaluated in order to provide the clearest path to success.

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Key points

- C3 glomerulopathies are rare diseases that share an underlying mechanism of complement dysregulation in the fluid phase and glomerular microenvironment.
- Diagnosis relies solely on renal biopsy immunofluorescence findings; light microscopy findings and complement biomarker profiles are heterogeneous.
- Acquired drivers, in the form of autoantibodies, are the abnormalities most frequently associated with complement dysregulation.
- Genetic variants in the *C3, CFB, CFH, CFI* and *CFHR1–CFHR5* genes are potentially causal; both rare and common variants can coexist and are associated with susceptibility to disease.
- Convertase dysregulation is central to the pathogenesis of C3 glomerulopathy.
- Conditions such as post-infectious glomerulonephritis cannot be differentiated from C3 glomerulopathy by renal biopsy alone, which can confound early diagnosis and treatment.

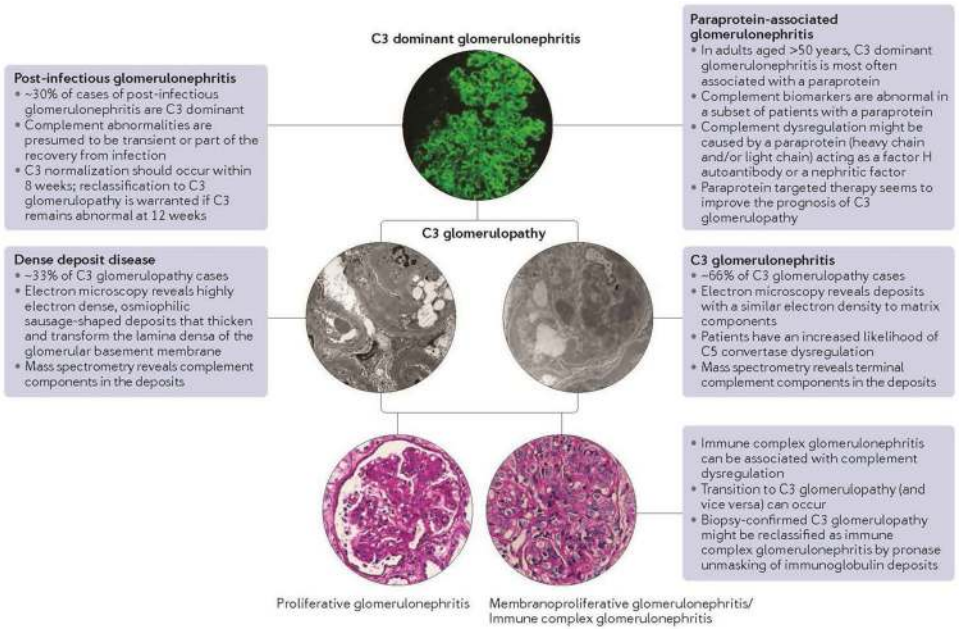

Figure 1. C3-dominant glomerulonephritis.

C3-dominant glomerulonephritis is a disease classification based on immunofluorescence findings of C3 staining that is at least 2 orders of magnitude more intense than that for any other immune reactant. Included in this definition are post-infectious glomerulonephritis and paraprotein-associated glomerulonephritis. In post-infectious glomerulonephritis, complement abnormalities are transient and C3 normalization typically occurs within 8 weeks; reclassification as C3 glomerulopathy is warranted if C3 levels remain abnormal at 12 weeks. Complement dysregulation occurs in a subset of patients with paraprotein-associated glomerulonephritis, perhaps because the paraprotein acts as a factor H autoantibody or nephritic factor. Paraprotein-targeted therapy improves the prognosis of C3 glomerulopathy in these patients. C3 glomerulopathy is a subtype of C3-dominant glomerulonephritis that can be subdivided into dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) on the basis of electron microscopy findings. In DDD, highly electron dense, osmiophilic sausage-shaped deposits thicken and transform the lamina densa of the glomerular basement membrane, and mass spectrometry reveals complement components in these deposits. In C3GN, the deposits have a similar electron density to matrix components, and mass spectrometry reveals that they contain terminal complement components. Patients with C3GN are more likely than those with DDD to have C5 convertase dysregulation. Light microscopy cannot distinguish C3 glomerulopathy from other forms of glomerulonephritis: findings are highly diverse, and include mesangial and endocapillary proliferative lesions, crescentic and membranoproliferative lesions. Complement dysregulation also underlies immune complex glomerulonephritis (ICGN), which can be distinguished from C3 glomerulopathy by pronase immunofluorescence, which unmasks immunoglobulin deposits. However, C3 glomerulopathy can transition to ICGN and vice versa.

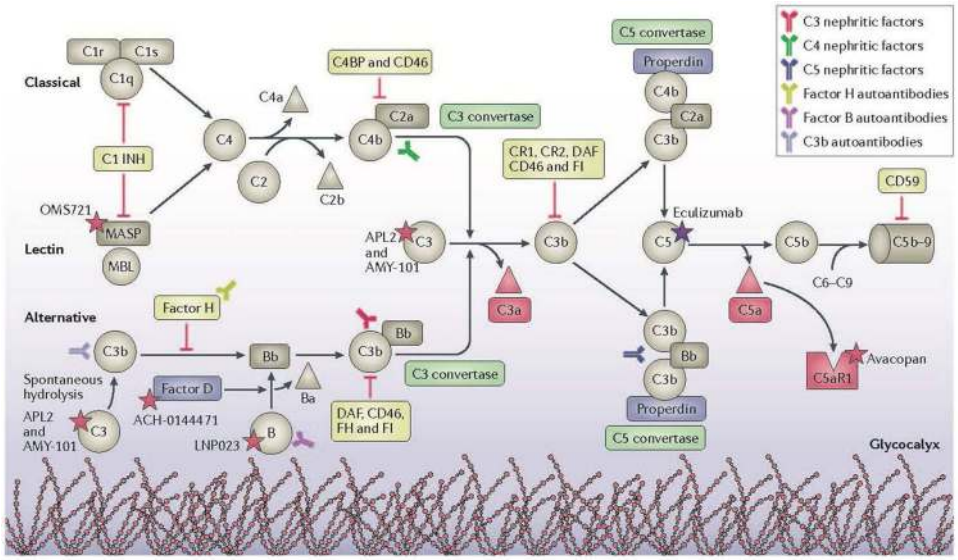

Figure 2. Dysregulation of the complement cascade in C3 glomerulopathy.

Complement is activated through the classical, lectin and alternative pathways, which lead to the formation of two C3 convertases. One C3 convertase (C4b2a) is associated with both the classical and lectin pathways, whereas the other (C3bBb) is associated with the alternative pathway. The two C3 convertases generate copious amounts of C3b, after which the pathways converge to generate large amounts of C3bBb. As more C3bBb forms, the terminal pathway is activated, primarily by generation of C3bBbC3b, a C5 convertase that cleaves C5 into C5a and C5b. However when the classical and lectin pathways are activated, C4b2aC3b, the C5 convertase of the classical and lectin pathways, is also formed. Complement activity results in generation of two potent anaphylatoxins, C3a and C5a (pink). In the majority (>90%) of patients with C3 glomerulopathy, dysregulation of the alternative pathway occurs in the fluid phase and in the glycocalyx overlying the glomerular endothelial pores (shown at the bottom of the figure). In the remainder (<10%) of patients with C3 glomerulopathy, dysregulation occurs at the level of the classical and/or lectin pathways. As a result of dysregulation, C3b deposited on the glycocalyx can serve as a substrate for C3 convertase formation and ultimately C5 convertase formation. Driving dysregulation are genetic changes (not shown) and/or autoantibodies to various pathway components and complexes. The targets of therapeutic agents currently under development are indicated by pink stars (the purple star is the site of action of eculizumab, which has already received approval); however, the complexity of the complement system and the heterogeneity of C3 glomerulopathy raise the possibility that no single treatment will be universally appropriate.

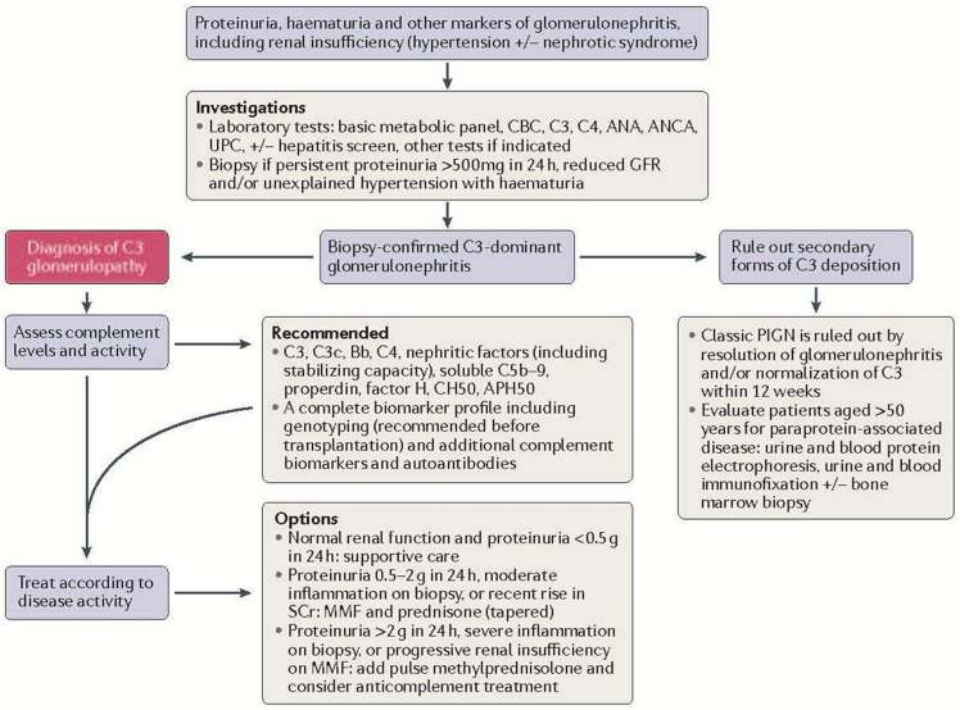

Figure 3. Diagnosis, evaluation and treatment of C3 glomerulopathy.

This algorithm presents a step-wise approach to the diagnosis, evaluation and treatment of C3 glomerulopathy. In the absence of robust predictive biomarkers and data from randomized controlled trials, this algorithm is based on the best evidence available and/or expert consensus. Patients presenting with proteinuria as well as haematuria and features of glomerulonephritis (such as renal insufficiency, hypertension and possibly nephrotic syndrome) undergo a standard battery of pre-biopsy laboratory tests. A biopsy finding of C3 dominant glomerulonephritis means that C3 deposition is at least 2 orders of magnitude greater than that for any other immunoreactant. However, this pathological diagnosis does not necessarily result in the diagnosis of C3 glomerulopathy. For example, infection can trigger a first episode of C3 glomerulopathy, which might confound the diagnosis of post-infectious glomerulonephritis (PIGN). By consensus, however, if all features of glomerulonephritis resolve by 12 weeks, the patient is not considered to have C3 glomerulopathy. Patients >50 years of age should be evaluated for the presence of paraproteins, which can trigger a predominant C3-deposition glomerulonephritis. If paraproteins are present, clone-guided treatment might improve renal outcomes; thus, a haematology consultation might be warranted (of note, paraproteins might also be present in patients <50 years of age). Once the diagnosis of C3 glomerulopathy is made, complement levels and activity should be evaluated to determine the degree of complement dysregulation, conduct disease staging, establish disease quiescence or progression, and determine transplant readiness. In the future, complement biomarkers might be key to choosing targeted therapeutics. Clinicians are, therefore, encouraged to conduct full complement function testing (biomarker measurement and interpretation are offered by several commercial laboratories) for all patients enrolled in clinical trials. Treatment depends on inflammation severity. Patients with mild inflammation receive glomerulus-focused

supportive care, including blood pressure control (to blood pressure <90th percentile in children and ≤120/80 mmHg in adults); use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, where possible, to control both blood pressure and urine protein excretion; optimal nutrition; and lipid control. In patients with moderate inflammation (that is, mesangial proliferative glomerulonephritis), treatment with mycophenolate mofetil (MMF) has been suggested by retrospective studies but is not uniformly successful. Severe inflammation (that is, marked membranoproliferative, endocapillary or crescentic glomerulonephritis) is treated by pulse methylprednisolone, perhaps with the addition of anti-complement agents. Although the evidence is insufficient to support a disease-specific versus an anti-inflammatory effect of eculizumab, isolated reports of some clinical benefit are associated with terminal complement blockade. No trials or other data consistently support a particular duration of prednisone therapy, but the authors of this Review caution against long-term steroid use and favour steroid-sparing agents. Finally, clinicians are encouraged to consider enrolling their patients in clinical trials of anti-complement therapies where safe and available. ANA, antinuclear antibodies; ANCA, antinuclear cytoplasmic antibodies; APH50, the serum dilution causing 50% lysis of rabbit erythrocytes in magnesium EGTA buffer; Bb, complement component; C, complement component; CBC, complete blood count; CH50, the serum volume or dilution causing 50% lysis of sensitized erythrocytes; GFR, glomerular filtration rate; UPC urinary protein:creatinine ratio; SCr, serum creatinine level.

Table 1.

Incidence and prevalence of C3 glomerulopathy

Study population	Incidence	Prevalence (point prevalence[a])	Comments	Refs.
19 patients (median age 21 years) with biopsy-proven C3 glomerulopathy from a referral population of 500,000 patients (UK; 2014)	1 in 1,000,000	1.3 in 10,000 (0.000132)	Data collected over a 17-year period Average life expectancy in the UK: 80 years	4
61 patients (median age 21 years) with biopsy-proven C3 glomerulopathy from a referral population of 2,000,000 people (Ireland; 2014)	2 in 1,000,000	1.1 in 10,000 (0.000109)	Data collected over a 17-year period Average life expectancy in Ireland: 82 years	4
134 patients (median age 24 years), all assumed to have C3 glomerulopathy, from 45 clinics (France; 2012)	0.2 in 1,000,000	0.14 in 10,000 (0.0000137)	Data collected over a 9-year period Average life expectancy in France: 82.5 years	5
141 patients assumed to have C3 glomerulopathy from a population of 1,140,000 people (Cyprus; 2011)	NR	1.4 in 10,000 (0.000137)	Data collected over a 17-year period (1984–2010) 10% of C3 glomerulopathy mutation carriers had a normal phenotype Average life expectancy in Cyprus: 79.6 years	6
111 patients (87 with C3GN and 24 with DDD; mean age 40 years) with C3 glomerulopathy from a tertiary referral centre (USA; 2018)	NR	0.05 in 10,000 (0.000005)	Data collected over a 20-year period Average life expectancy in US: 79 years	3

[a]Point prevalence values were calculated as (*n* cases/*n* referral population) × (population average life expectancy – median or mean age of case patients)/*n* years of data collection. For all calculations, we assumed that there were no deaths from C3 glomerulopathy, that the referral population remained stable over time, and that the diagnostic rate remained stable over time and throughout life. C3GN, C3 glomerulonephritis; DDD, dense deposit disease; *n*, number; NR, not reported.

Table 2.

Animal models of C3 glomerulopathy

Genotype	Phenotype	Renal phenotype	Refs.
Pig model			
Norwegian Yorkshire homozygous for Ile1166Arg mutation in factor H	Deficient in factor H secondary to a defect in protein secretion	DDD	30
Mouse model			
Cfh$^{-/-}$	Deficient in factor H	Glomerular C3 staining on immunofluorescence; C3GN	31
Cfh$^{-/-}$*Cfb*$^{-/-}$	Deficient in factors H and B	No evidence of C3GN on light microscopy	31
Cfh$^{-/-}$*C5*$^{-/-}$	Deficient in factors H and C5	C3GN less pronounced than in *Cfh*$^{-/-}$ mouse, reduced mortality, reduced glomerular hypercellularity and decreased serum creatinine levels	34
Cfh$^{-/-}$*Cfi*$^{-/-}$	Deficient in factors H and I	No evidence of C3GN on light microscopy; mesangial C3 staining on immunofluorescence	35
Cfh$^{-/-}$*Itgam*$^{-/-}$	Deficient in factors H and complement receptor type 3 α-chain	Increased severity of spontaneous glomerular injury	36
Cfh$^{-/-}$*P*$^{-/-}$	Deficient in factor H and properdin	Enhanced glomerular injury with increased glomerular C3 accumulation	32
Cfh$^{m/m}$*P*$^{-/-}$	Deficient in factor H and properdin Circulating factor H lacks the last two terminal short consensus repeats	Enhanced glomerular injury with DDD-like disease and increased glomerular C3 accumulation	33
Cfi$^{-/-}$	Deficient in factor I	Glomerular hypercellularity, capillary wall thickening and mesangial expansion in some animals; mesangial C3 staining on immunofluorescence	35

C3GN, C3 glomerulonephritis; DDD, dense deposit disease

Table 3.

FHR fusion proteins in familial C3 glomerulopathy

Protein name	Protein structure	Phenotype	Comments	Refs.
Normal proteins				
FHR1		NA	Homodimerizes and heterodimerizes with FHR2; competitive antagonist of factor H; C5 convertase inhibitor and terminal complement cascade blocker	42
FHR2		NA	Homodimerizes and heterodimerizes with FHR1; competitive antagonist of factor H; C3 convertase inhibitor	43
FHR3		NA	Exact function unknown	NA
FHR5		NA	Homodimerizes; competitive antagonist of factor H; binds to extracellular matrix; complement amplifier and surface anchor for properdin	44
Fusion proteins				
$FHR2_{1,2}$–$FHR5_{1–9}$		DDD	Normal gene copies present in variant allele: *CFHR3, CFHR1, CFHR4*	45
$FHR5_{1,2}$–$FHR5_{1–9}$		C3GN	Normal gene copies present in variant allele: *CFHR3, CFHR1, CFHR4, CFHR2, CFHR5*	4,46
$FHR3_{1–2}$–$FHR1_{1–5}$		C3GN	Normal gene copies present in variant allele: *CFHR3, CFHR1, CFHR4, CFHR2, CFHR5*	47
$FHR1_{1,2}$–$FHR5_{1–9}$		C3GN and/or DDD	Normal gene copies present in variant allele: *CFHR3, CFHR5*	48
$FHR1_{1–4}$–$FHR1_{1–5}$		C3GN	Normal gene copies present in variant allele: *CFHR3, CFHR4, CFHR2, CFHR5*	35
$FHR5_{1,2}$–$FHR2_{1–4}$		C3GN	Normal gene copies present in variant allele: *CFHR3, CFHR1, CFHR4, CFHR2, CFHR5*	36

FHR proteins contain several complement control domains, also termed short consensus repeats (SCRs). FHR1, purple, contains five SCRs (1–5). FHR2, pale blue, contains four SCRs (1–4). FHR3, green, contains five SCRs (1–5). FHR5, orange, contains nine SCRs (1–9). The same SCR numbering is used in the fusion proteins. C, complement component; C3GN, C3 glomerulonephritis; DDD, dense deposit disease; NA not applicable.

Table 4.

Acquired drivers of C3 glomerulopathy

Driver	Frequency in affected patients (%)	Function	Knowledge gaps	Refs.
C3 nephritic factors	50–80	Dysregulation of C3 convertase (C3bBb)	• Diagnostic assays need standardization • In vitro function of antibodies well characterized however well documented in vivo data supporting cause-and-effect relationship to disease needed • Not known whether antibody characteristics change over disease course • Unclear why antibody removal methods (plasma exchange or B-cell targeted agents) are generally not effective • Defining the mechanism underlying complement dysregulation is often very difficult	56
C4 nephritic factors	2.4	Dysregulation of C3 and C5 convertases of the classical and lectin pathways (C4b2a and C4b2aC3b)		56
C5 nephritic factors	50	Dysregulation of C5 convertase (C3bBbC3b)		57
Factor H autoantibodies	~1	Affects factor I cofactor activity; not associated with *CFHR3* or *CFHR1* gene deletion		58
Factor B autoantibodies	~2.5	Recognizes the Bb fragment; binds C3 convertase; increases release of C3a and Bb; does not enhance C5 convertase activity		59
C3b autoantibodies	1.5	Recognizes C3b and C3c; stabilizes C3 convertase; reduces binding to complement receptor type 1; increases activity of C5 convertase		59
Monoclonal immunoglobulins	Sporadic cases of multiple myeloma or MGRS	Intact antibody and/or light chain fragments interfere with alternative pathway regulation		60-62

C, complement component; MGRS, monoclonal gammopathy of renal significance.

Table 5.

Novel therapeutic agents that target complement activity

Drug	Target	Mechanism	Clinical trial number
ACH-0144471	Factor D	Prevents formation of C3 and C5 convertases	, ,
LNP023	Factor B	Prevents formation of C3 and C5 convertases	Not yet registered
APL2	C3	Prevents formation of C3 and C5 convertases	
AMY-101	C3	Prevents formation of C3 and C5 convertases	
OMS721	MASP-2	Blocks initiation of lectin pathway	
Eculizumab	C5	Blocks progression of terminal pathway	Off-label use
Avacopan	C5aR1	Blocks anaphylatoxin formation (C3a, C4a and/or C5a)	

No clinical trials of drugs that enhance complement regulation are currently ongoing in patients with C3 glomerulopathy.