REVIEW

Reclassification of membranoproliferative glomerulonephritis: Identification of a new GN: C3GN

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Abstract

This review revises the reclassification of the membranoproliferative glomerulonephritis (MPGN) after the consensus conference that by 2015 reclassified all the glomerulonephritis basing on etiology and pathogenesis, instead of the histomorphological aspects. After reclassification, two types of MPGN are to date recognized: The immunocomplexes mediated MPGN and the complement mediated MPGN. The latter type is more extensively described in the review either because several of these entities are completely new or because the improved knowledge of the complement cascade allowed for new diagnostic and therapeutic approaches. Overall the complement mediated MPGN are related to acquired or genetic cause. The presence of circulating auto antibodies is the principal acquired cause. Genetic wide association studies and family studies allowed to recognize genetic mutations of different types as causes of the complement dysregulation. The complement cascade is a complex phenomenon and activating factors and regulating factors should be distinguished. Genetic mutations causing abnormalities either in activating or in regulating factors have been described. The diagnosis of the complement mediated MPGN requires a complete study of all these different complement factors. As a consequence, new therapeutic approaches are becoming available. Indeed, in addition to a nonspecific treatment and to the immunosuppression that has the aim to block the auto antibodies production, the specific inhibition of complement activation is relatively new and may act either blocking the C5 convertase or the C3 convertase. The drugs acting on C3 convertase are still in different phases of clinical development and might represent drugs for the future. Overall the authors consider that one of the principal problems in finding new types of drugs are both the rarity of the disease and the consequent poor interest in the marketing and the lack of large international cooperative studies.

Key words: Glomerulonephritis reclassification; Dense deposit disease; Membranoproliferative glomerulonephritis; C3 glomerulopathies; Targeting complement pathways; Complement dysregulation

Core tip: The complement pathway dysregulation has been recognized as the main cause of some membrano-proliferative glomerulonephritis (MPGNs). This fact is at the basis of the new classification of the disease and of the findings of new entities as the complement factor H related protein nephropathy. Genetic studies as well as improvement in proteomics allowed recognizing the complement dysregulation as the cause of some renal diseases as the MPGN and the atypical hemolytic uremic syndrome that may be considered as strictly related diseases. The anti-complement drugs represent a new approach in the treatment of these diseases and their use in larger evidence based randomized trials is required.

INTRODUCTION

By 2015, nephrologists and renal pathologists held a consensus meeting to formulate a new etiology/pathogenesis-based system to classify glomerulonephritis (GN)[1]. According to the consensus report, GNs have been classified into five etiology/pathogenesis-based categories (Table 1).

According to the new classification, membrano-proliferative GNs (MPGN) have been reclassified and divided into different chapters on the basis of pathophysiology. In addition, new entities have been found. This review will discuss the new classification of MPGNs and will principally describe the complement-dysregulation dependent C3 glomerulopathies (C3G).

MPGN

Until recently, the MPGNs have been distinguished according the histological and ultra structural findings and were classified as MPGN type Ⅰ, type Ⅱ and type Ⅲ. The glomerular lesions include mesangial hypercellularity, endocapillary proliferation and duplication of glomerular basement membrane (GBM) lesions[2]. Sub-endothelial and mesangial deposits are predominant in MPGN type Ⅰ[3]. Highly osmophylic electron-dense intramembranous deposits characterize type Ⅱ GN[4], which is also known as dense deposits disease (DDD). In type Ⅲ MPGN deposits may be found in the sub-endothelial and sub-epithelial spaces[5].

With the discovery of the complement role in generating glomerular diseases[6], a new classification of MPGN was developed, based on pathophysiology and considering whether immunoglobulins accompany the complement using immunofluorescence on biopsy specimens[7,8] (Figure 1).

This new classification resulted in three principal consequences: (1) to identify new entities, which until now were unknown or misdiagnosed; (2) to highlight new diagnostic approaches. Indeed in the case of Ig-mediated MPGN, a work-up for infections, autoimmune diseases and monoclonal gammopathies should be adopted. In the case of complement-mediated GN, a complete study of the complement alternative pathway (AP) should be performed; and (3) to differentiate the therapeutic approach according to the type of MPGN. In summary, the three different forms of MPGN are now recognized as follows: (1) Immunocomplexes-associated MPGN with complement over activation (old MPGN type Ⅰ); (2) MPGN with intramembranous dense deposits (old MPGN type Ⅱ); and (3) C3GN, a new entity complement-mediated GN. DDD and C3GN are both related to complement dysregulation and are "*de facto*" included in the same chapter.

IMMUNOCOMPLEXES ASSOCIATED MPGN

Immune-complexes mediated MPGN is caused by the deposition of immunocomplexes in the glomeruli. The immunocomplexes activate the classical pathway (CP) of complement and cause the deposition of complement factors or of the membrane attack complex (MAC) in the mesangium and capillary loops[9].

The MPGN is an uncommon cause of nephropathy (approximately 5 per million persons per year) and is more often secondary to infections, autoimmune disease and monoclonal gammopathy[10].

Pathophysiology

MPGN and infections: Hepatitis C and B, which are often accompanied by circulating cryoglobulins, are a frequent cause of MPGN[11-14]. In addition, chronic bacterial infections, fungal and parasitic infections may also cause MPGN[15-17].

Immunocomplexes depositions are the first step. Consequently, CP is activated and in addition to the direct damage cause by MAC, C3a and C5a are generated that favor leukocyte accumulation, cytokine release and a further glomerular damage.

MPGN and autoimmune diseases: Mixed cryoglo-bulinemia is frequently associated with hepatitis C infection, systemic lupus erythematosus, sclerodermia, Sjögren syndrome and rheumatoid arthritis. These are the autoimmune diseases that more frequently cause MPGN due to the persistence of circulating immunocomplexes[18-21]. Under these conditions, circulating immunocomplexes may also activate the complement CP with the abovementioned subsequent events described for MPGN due to infections.

MPGN and monoclonal gammopathy: The renal deposition of monoclonal immunoglobulins (MIg) may determine a wide spectrum of renal lesions as recently

Table 1 Classification of glomerulonephritis

Pathogenetic type	Specific disease entity	Pattern of injury: Focal or diffuse	Score or class
Immune-complex GN	IgA nephropathy, IgA vasculitis, lupus nephritis, infection-related GN, fibrillary GN with polyclonal Ig deposits	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing or multiple	Oxford/MEST scores for IgA nephropathy ISN/RPS class for lupus nephritis
Pauci-immune GN	MPO-ANCA GN, proteinase 3-ANCA GN, ANCA-negative GN	Necrotizing, crescentic, sclerosing, or multiple	Focal, crescentic, mixed, or sclerosing class (Berden/ EUVAS class)
Anti-GBM GN	Anti-GBM GN	Necrotizing, crescentic, sclerosing, or mixed	
Monoclonal Ig GN	Monoclonal Ig deposition disease, proliferative GN with monoclonal Ig deposits, immunotactoid glomerulopathy, fibrillary GN with monoclonal Ig deposits	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing or multiple	
C3 glomerulopathy	C3 GN, dense deposit disease	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing or multiple	

GN: Glomerulonephritis; MEST: Mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis, interstitial fibrosis/tubular atrophy; ISN/RPS: International Society of Nephrology/Renal Pathology Society; MPO: Myeloperoxidase antibodies; ANCA: Antineutrophil cytoplasmic antibodies; EUVAS: European vasculitis study group; GBM: Glomerular basement membrane.
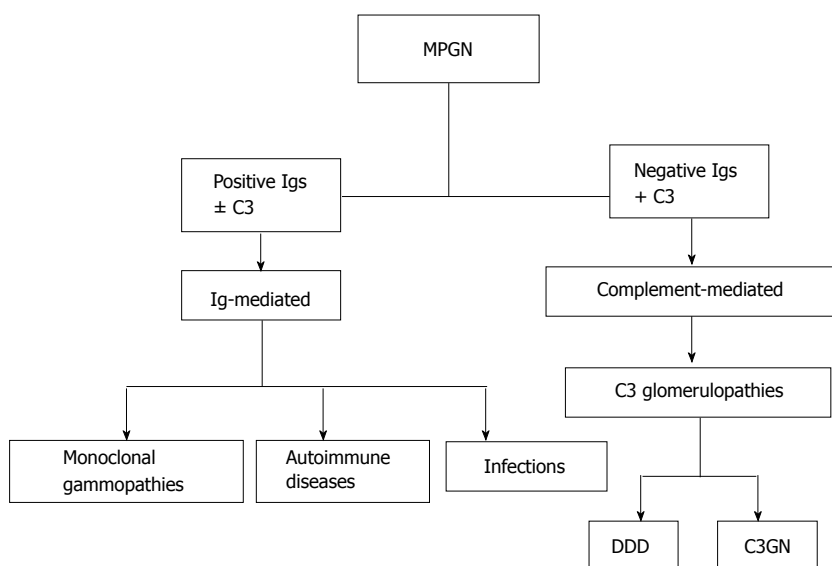

Figure 1 Proposed classification for membrano-proliferative glomerulonephritis based on the presence or absence of Igs and the presence of C3 by immunofluorescence. MPGN: Membranoproliferative glomerulonephritis; Igs: Immunoglobulins; DDD: Dense deposit disease.

described[22]. Monoclonal gammopathy as well as light chain and heavy chain diseases may result in MPGN[23]. These lesions may hide a variety of severe hematological diseases ranging from low-grade B cell lymphoma, chronic lymphocyte leukemia to multiple myeloma[9]. In a recent monocenter study of MIg-associated MPGN after excluding infections and autoimmune disease, 26 out of 28 patients were serum electrophoresis-positive and 27 out of 28 patients were urine electrophoresis-positive[24]. In this monocentric study, out of 126 patients affected by MPGN, 41% were urine- or serum-positive for monoclonal gammopathy.

Monoclonal gammopathies are associated with complement activation; indeed, the abnormal immunoglobulin might activate the AP[10].

Recently, cases of C3 glomerulopathies, including C3GN and DDD (see below) associated with MIgs have been described[25]. In these patients the monoclonal immunoglobulin causes a complement dysregulation by interfering with the function of complement-regulating proteins, such as factor H or acting as an autoantibody against factor H or factor B[26-28].

Clinical and therapy
Immunocomplex-mediated MPGNs principally affect children and young adults. Its clinical presentation may range from nephrotic syndrome and acute nephritic syndrome, to asymptomatic proteinuria and hematuria. Renal dysfunction frequently occurs, and 40% of the patients progress to end stage renal disease (ESRD) in approximately 10 years.

The efficacy of the different therapeutic approach is difficult to evaluate due to the small number of patients and because several trials include the three different types of MPGN[29,30]. The therapy most widely used is based on anti-cell proliferation agents[31]. Over-
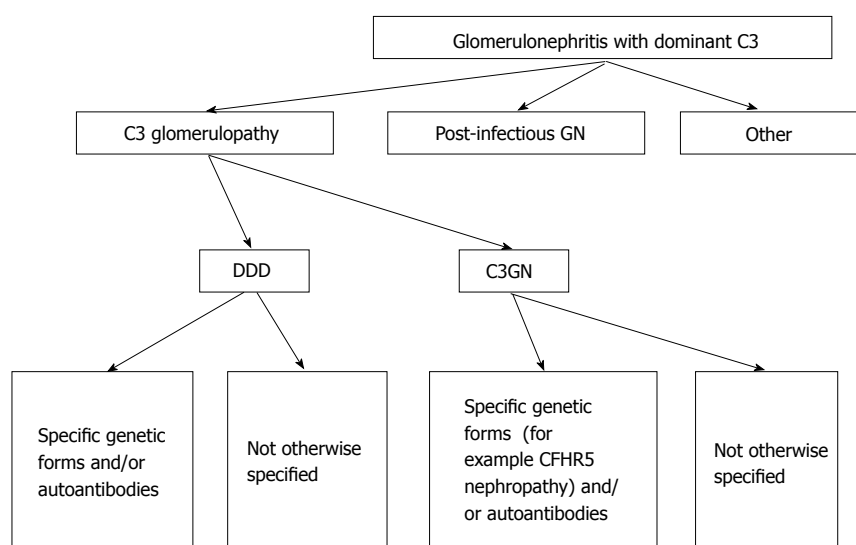
Figure 2 **Approach to the classification of glomerulonephritis with dominant C3.** DDD: Dense deposit disease; CFHR5: Complement factor H related protein.

activation of complement is often present, but whether anticomplement drugs might be useful in this context remains to be elucidated.

According to different studies, renal transplantation is a viable option in patients with ESRD, even if the disease recurs after transplantation with a frequency ranging from 27% to 65%[32-34]. In a recent study, after the exclusion of patients with DDD, a recurrence rate of 41% has been reported[34]. Such a high recurrence rate has been confirmed by a study published in 2016, which evaluated the recurrence rate using the new classification[35]. In another study the recurrence of Ig-mediated MPGN was lower (23.5%) and after a follow-up of 15 years, the graft survival rate of MPGN patients was similar to those of controls affected by different diseases[36].

COMPLEMENT MEDIATED MPGN

MPGN patients that have on renal biopsy clear glomerular C3 staining with few or no immunoglobulin deposition are referred to as complement-mediated MPGN and are defined as C3G. C3Gs are less common than immune-complex-mediated MPGNs and are further divided into two groups according to the presence or absence of highly electron-dense deposits into the GBM.

The disease with intramembranous deposits corresponds to the DDD (previously called MPGN type Ⅱ). The disease without dense deposits, with C3 prevalence and no Igs on the glomeruli and with MPGN aspect on normal histology, is referred to a recently recognized entity: the C3GN. The distinction between the two diseases often requires the use of electron microscopy. C3GN was initially described by Servais *et al*[37] who described a series of 19 patients and proposed the term C3GN to highlight a disease that is characterized by C3 prevalence on the glomeruli, without intramembranous deposits. In addition, Servais *et al*[37] observed that this new entity often shares common genetic risk factors with atypical hemolytic uremic syndrome (aHUS).

Overall the term C3G was introduced to define all MPGNs that are characterized by the prevalence of C3 in the glomeruli[38], including DDD.

The term C3G has also been introduced because C3 isolated accumulation was recognized to include several heterogeneous entities and due to our improvement in the understanding of complement-mediated kidney injuries. Consequently, several complement factor abnormalities resulting in glomerular lesions have been identified. In 2013, a first consensus meeting on C3G was held to better clarify the pathogenic aspects and terminology[39]. The consensus conference resulted in an improved classification (Figure 2) that also documented that need of future work.

C3G are all caused by dysregulation of the complement AP and of the terminal complement complex (TCC)[40] (Figure 3).

Clinical features

DDD has an estimated prevalence of 2 to 3 per million populations[41] and prevails in childhood and in young adults[42]. C3GN prevalence is difficult to be evaluated, as this disease is new and as time progresses, more patients are identified with family studies and with an improvement in the Genetic wide association studies.

Overall, patients affected by DDD are younger with respect to patients affected by C3GN[43]. Both diseases affect males and females with the same frequency[44-46]. Renal manifestations are similar in DDD and C3GN[43] and include hypertension, hematuria and proteinuria more often in the nephrotic range. Non renal manifestations of DDD include ocular lipoproteinaceous deposition and acquired lipodystrophy[47,48].

MIg in the serum may also be associated with both DDD and C3GN[25,49-51]. These patients often have a poor renal prognosis.

Progression to ESRD is common in both DDD and C3GN. Renal transplantation is feasible but with a high rate of disease recurrence[52].
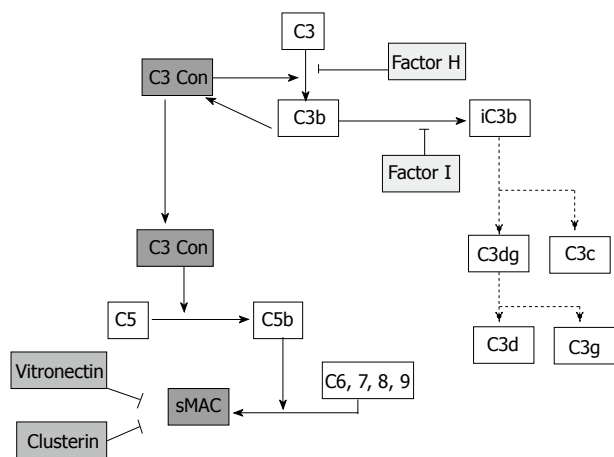
Complement factor H related protein (CFHR5)

Figure 3 Pathway of complement and complement regulator factors. C3 Con: C3 covertase; sMAC: Serum membrane attack complex; C3dg, C3c, C3d, C3g: Complement degradation products.

nephropathy is a subtype that is well identified in C3GN caused by the presence of an abnormal CFHR5 protein. The disease is inherited and was first identified in Cypriot families[53]. The disease may often occur with clinical manifestations that are similar to IgA nephropathy with microscopic hematuria or macroscopic hematuria after an acute upper respiratory tract disease[54]. Progression to ESRD is common. Interestingly, ten patients affected by CFHR5 nephropathy received a successful renal transplantation[54].

Pathophysiology

Dyregulation of the complement AP may occur principally due to acquired or genetic abnormalities[9] (Figure 4).

The auto-antibodies are the most frequently acquired abnormality. Auto-antibodies may be directed against the complement-regulating factors, such as factor H, factor I, factor B as well as against C3 convertase itself[55,56].

The first described autoantibody was the C3 nephritic factor (C3 NeF), which binds and stabilizes C3 convertase[57]. A second type of C3 NeF properdin dependent has also been described[58]. C3 NeFs are principally present in patients affected by DDD but are less frequently found in C3GN and absent in CFHR5 nephropathy[43].

In DDD, auto-antibodies that bind factor B and target C3B have been described in patients affected by MPGN type Ⅱ[56,59]. Anti CFH auto-antibodies have also been found in patients affected by DDD and C3GN[60,61].

Anti CFH auto antibodies are also frequently present in aHUS. A recent study[62] highlights that anti-factor H antibodies are equally present in C3G and aHUS, but that the auto-antibody structure is different in the two diseases. Indeed, in C3G, the auto-antibody principally binds to the amino terminal domains, while in aHUS, it binds to the carboxyterminal domain[10]. As previously mentioned, the two diseases are strictly related, but several differences are present.

The discovery of familial cases of C3G highlights that

in several cases, a familial genetic basis of the disease occurs.

In 2010, Martínez-Barricarte *et al*[63] described a family in which some members were affected by a mutant form of C3 resistant to cleavage by C3 convertase. Consequently, this caused an AP dysregulation restricted to the fluid phase and these patients continuously produced and consumed C3 produced by the normal *C3* allele. These patients were affected by the classic DDD. Complement factor H-related (*CFHR*) genes are often involved. There are five CFH-related proteins (CFHR1-5 and genetic abnormalities of these proteins have been recognized and may cause disease. Recently, Chen *et al*[64] described two patients from the same family affected by DDD and with an abnormal deletion in the complement factor H-related (*CFHR*) gene cluster. This resulted in a hybrid CFHR protein that inhibited the complement decay-factor H-mediated.

Another genetic cause of C3G has been reported by Gale[53]. Gale *et al*[53] described two families of Cypriot origin whose members were affected by a mutation in CFHR protein 5. These patients were affected by a C3G that was defined as CFHR5 nephropathy. Indeed, genome-wide linked analysis (GWLA) allowed localization of a genetic abnormality in chromosome 1q31-32. In these patients, a larger CFHR5 protein is generated that is less effective in associating with surface-bound C3b. The resulting disease was known as CFHR5 nephropathy.

Recently, Malik *et al*[65] described an autosomal dominant complement-mediated C3G associated with abnormal copies in the *CFHR3* and *CFHR1* loci.

Finally, Habbig *et al*[66] described two siblings affected by renal disease. Both children had a homozygous deletion of 224 lysine of CFH. This deletion led to a defective complement control[67]. The renal disease was compatible with C3G. The authors proposed the name of C3 deposition glomerulopathy (C3DG) due to the absence of DDD.

Overall, these families highlight the genetic origin of several C3Gs related to a dysregulation of the AP and TCC.

Summarizing, the disease mechanisms in C3G caused by genetic defects identified in family studies may be classified into three categories: (1) homozygous deficiency dysfunction of CFH resulting in excessive C3 activation; (2) hyperfunctional C3 producing excessive C3 activation despite normal CFH activity; and (3) abnormal CFHR protein that enhances CFH dysregulation and consequent excessive C3 activation.

Diagnosis

The diagnosis of C3G and differential diagnosis between DDD and C3GN should include a comprehensive pathological analysis and a complete work-up on the genetic and biochemical aspects of complement pathways, with particular regard to the AP.

Using light microscopy, in the case of C3 prevailing without Ig on glomeruli, only a suspicious diagnosis of
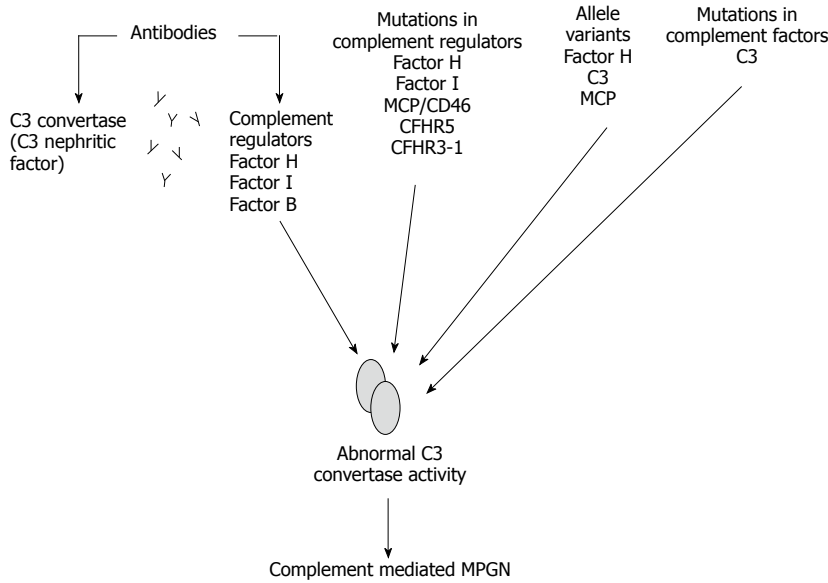
Figure 4 Acquired and genetic abnormalities associated with complement-mediated membranoproliferative glomerulonephritis. MCP: Membrane cofactor protein; CHFR: Complement factor H related proteins; MPGN: Membranoproliferative glomerulonephritis.
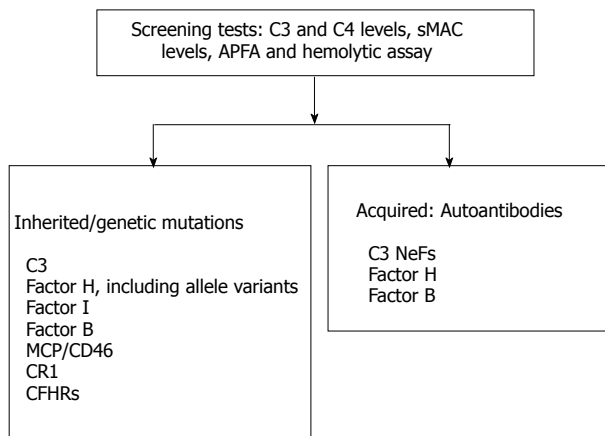

Figure 5 Proposed work-up of complement mediated membranoproliferative glomerulonephritis. APFA: Alternative pathway functional assay; CFHR: Complement factor H related proteins; CR1: Complement receptor 1; MCP: Membrane cofactor protein; sMAC: Serum membrane attack complex; MPGN: Membranoproliferative glomerulonephritis.

C3G may be formulated. The definitive diagnosis might only rely on ultra-structural basis.

Overall DDD, is characterized by dense osmiophilic band-like deposits within the GBM. C3GN may be characterized by sub endothelial and mesangial deposits, though intramembranous and sub epithelial deposits may also be present[68]. Several patients may present an overlap in the ultra-structural findings and are difficult to be classified. Proteomic studies may be useful for their identification[50,69].

The evaluation of the complement AP is essential for an improved diagnosis. The evaluation may be performed in several ways: (1) evaluating the total hemolytic complement assay[70]; (2) evaluating the complement alternative pathway assay[71]; and (3) evaluating the complement factor H functional assay[72].

In addition, the C3, C4 and serum MAC (sMAC) levels should be determined. In the case of positivity of these tests, genetic and enzyme-linked immunosorbent assays for complement abnormalities should be performed[8] (Figure 5).

Mutations in the *CFH*, *CFI* and *CD46* genes have been reported in some patients affected by DDD[39,43]. Changes in factor *B* and *C3* genes may also be present[56,63]. In CFHR5 nephropathy, an internal duplication in the *CFHR5* gene is present[53]. Other rearrangements of the *CFHR2-CFHR5* hybrid gene and other abnormalities in *CFHR1* and *CFHR5* have been reported[73-75].

An interpretation of identified variants may be difficult to be understood for several reasons[76]. The pathogenic variants accounts for only 25% of patients affected by DDD and C3GN[43,46]. In addition, mutations in other genes, such as thrombomodulin (*THBD*), diacylglycerol kinase-epsilon (*DGKE*), and the *CFHR* gene family have been recently found to be implicated to contribute to these diseases[77,78].

Moreover, further studies did not confirm a pathogenic role for several missense variants that were originally thought to be at the basis of the disease. Consequently, several amino acid changes in the gene structure are not "*de facto*" related to the disease[79].

Finally, most variants have a low penetrance and combined variants have been reported in 3% to 12% of patients[80].

The non-genetic causes of C3G are principally auto-antibodies: (1) C3 NeF: It binds directly to C3 convertase prolonging its survival. C3NeFs are found in 80% of patients affected by DDD and in 50% of patients affected by C3GN[43,59]. A C3NeF can stabilize C5 convertase in addition to C3 convertase, which has been previously described[81]. The detection of C3 NeF may be performed in several ways[82]. Further studies are needed to better correlate the presence of C3 NeF with the cause of the diseases and with treatment efficacy; (2) C4 NeF: The role of C4 NeF is still unclear, even if this auto-antibody has been found in some patients affected by MPGN[83]; (3)Anti-factor H auto-antibodies: Have been described

Table 2 Complement testing in patients with C3 glomerulopathy

Test	Interpretation	Limitations
C3 and C4 levels	C3 frequently depressed and support diagnosis; Normal C4 suggests an alternative pathway process	Non-specific
Soluble C5b-9	May be indicator of active disease; May identify patients who will benefit from C5 blockade	Test not widely available
C3 nephritic factor	Associated with C3 glomerulopathy; May identify patients who will benefit from B cell targeted therapies	Levels do not correlate with disease activity; also seen in MPGN type I
Factor H protein levels	May identify underlying mechanism of alternative pathway activity; May identify patients who will benefit from plasma infusion/exchange	
Autoantibodies to factor H and factor B	May identify underlying mechanism of alternative pathway activity; May identify patients who will benefit from B cell targeted therapies	Test not widely available
Genetic mutation screening Factor H CFHR1, 2, and 5 Factor I C3 Factor B	May identify underlying mechanism of alternative pathway activity	Not widely available; Clinical implications unknown

MPGN: Membranoproliferative glomerulonephritis; CFHR: Complement factor H related proteins.

Table 3 Possible treatment of C3 glomerulopathies

Nonspecific treatment
Replace deficient gene products
  Plasma infusion
  Liver Transplantation
Eliminate autoantibodies and/or mutant proteins
  Plasma exchange
  Immunosuppression
  Treatment of plasma cell dyscrasia
Inhibition of complement activation
  Eculizumab (anti C5)
  Inhibition of the C3 Convertase
Renal transplantation
New trials ongoing

in patients affected by DDD[41] and C3GN[46]. They may be detected using an enzyme-linked immunosorbent assay. If an anti-factor H is found, then monoclonal gammopathy should be excluded principally in older people[28,50]; and (4) Anti-factor B auto-antibodies are not frequently found and their research by enzyme-like immunosorbent assay is not easy and is often not available[56]. Overall, the suggested complement investigations in C3G are indicated in Table 2 as suggested by the previously cited consensus report[39].

Treatment

Several treatments for C3Gs may be attempted. According to evidence-based medicine, to date, most of the treatments have not yet been proven to be effective in C3G (Table 3).

Non-specific or supportive measures: By extrapolating from the treatment of other chronic renal diseases, blood pressure control, reduction of proteinuria and the lowering serum lipid levels should have a beneficial effect in patients affected by C3G, and principally in those affected by a low disease progression[46].

In the previously mentioned French study[43], the renin-angiotensin-aldosterone system (RAAS) blockade was associated with prolonged renal survival, but these findings have not been confirmed by a United States study[49]. In the latter study, the RAAS blockade had beneficial effects only when associated with steroids. In another study, Maisch *et al*[84] documented the efficacy of a lipid-lowering strategy by statins.

Replacement of deficient gene products: Due to the unavailability of purified complement regulating factors, often a functioning factor may be administered by plasma infusion. The limitation is the need of lifelong substitution therapy.

Plasma infusion is not beneficial in patients affected by a mutation in the membrane cofactor protein because the factor is membrane-bound and not circulating[85]. Plasma infusion is similarly ineffective or even contraindicated in patients affected by gain-of-function mutations or in patients affected by a C3 convertase resistant to factor H[63]. Because CFH, CFI, CFB and C3 are produced by the liver, a simultaneous liver-kidney transplantation may be effective and therapeutically useful[86].

In consideration of frequent short-term complications, of the mortality rate of 15% and of the growing experience with eculizumab, an anti-complement drug, a combined liver-kidney transplantation will lose indication[87,88].

Elimination of the auto-antibodies and/or mutant protein: The use of plasma exchange has a strong rationale[89], but to date, its efficacy has only been confirmed by single case reports. Three patients with DDD had a beneficial effect from plasma exchange, but they were also treated with immunosuppression[90-92]. However, McCaughan *et al*[93] reported the lack of efficacy of plasma exchange, despite the complete removal of C3NeF. Moreover, in the eculizumab era, the plasma exchange will continue to be used after evaluation of individual patients.

Efficacy of immunosuppression is not yet established.

Treatment with steroids led to a clinical improvement in children affected by C3G treated on the basis of a renal biopsy, revealing signs of acute glomerular inflammation with crescents, but a similar improvement was similarly observed in non-treated patients[94]. The combination of steroids with other immunosuppressants has been reported to have a higher beneficial effect[95-97]. These effects have been principally documented in the aHUS. Treatment with an anti-CD20 monoclonal antibody has been effective in one patient affected by DDD with documented anti-CFB auto-antibodies[59].

Very recently, the beneficial effect of mycophenolate mofetil (MMF) in C3G has been reported in a randomized Spanish study[98]. However, due to the lack of controlled trials, treatment with immunosuppressants should be restricted to patients with proteinuria, progressive loss of glomerular filtration rate (GFR) and those with signs of severe inflammation on renal biopsy[89].

An immunosuppressant-based strategy should also be attempted in patients with C3G associated with monoclonal gammopathy, even if the result of such a treatment differed according to different authors[50,51].

Inhibition of complement activation: The most adequate approach to the treatment should be the complement cascade blockade. Eculizumab is a recombinant, fully humanized monoclonal antibody that binds to the C5 complement protein and blocks C5 cleavage[89]. In recent years, eculizumab was highly effective in several kidney diseases, including aHUS and antibody-mediated rejection (ABMR) after renal transplantation[99]. The efficacy of eculizumab in C3Gs to date is only based on the report of single patients, on an open label proof of concept study in 6 patients, and on one ongoing randomized clinical trial (RCT) whose results are unknown to date[100]. Overall, 14 patients affected either by DDD or C3GN treated with eculizumab have been reported. Eight of these patients were described in single case reports and the treatment was successful in seven patients[93,101-107]. In addition to the clinical response, an improvement in renal histology has been observed in patients who underwent a repeated renal biopsy. However, such good results were not confirmed by the proof-of-concept study[108,109]. In this study, a clinical response to eculizumab has been observed in only three patients.

Furthermore, in a recent study, three more patients affected by rapidly progressive C3G have been reported[110]. All these patients responded to eculizumab with an improvement in renal function, a regression of proteinuria and an improvement of glomerular lesions. The phenotypic expression of C3G (DDD vs C3GN) does not predict the response to treatment, even if in biomarkers studies, a higher terminal pathway activity in C3GN has been found[111].

Overall, these results revealed disparate results to the treatment and highlight the possibility that complement dysregulation is not always the same in these patients

and that in some of the patients, a resistance to C5 cleavage blockade might exist. The unresponsiveness to eculizumab may have different explanations.

Recently, Nishimura et al[112] documented that some patients affected by paroxysmal nocturnal hemoglobinuria (PNH) had a missense mutation at arginine 885 at the level of the *C5* gene. This mutation caused a resistance to C5 cleavage by eculizumab.

In addition, patients affected by C3G, after eculizumab administration, may have a persistent fluid phase C3 convertase activity in the absence of terminal complement activity, which has been documented in a patient with C3G caused by a hybrid CFHR2/CHFR5 protein[64]. In this patient, after eculizumab administration, a block of C5 cleavage and sMAC generation has been obtained, but the hyperfunctioning C3 convertase remained active. Consequently, patients with a C3 convertase dysregulation greater than C5 dysregulation should not be treated with C5 blockade[113]. Moreover, has been documented that this block might aggravate the C3 convertase activity *via* a feed-back mechanism. Consequently, patients affected by C3G with a prevailing C3 convertase activity should be treated with drugs inhibiting C3 convertase. Blocking the complement AP at the C3 level might be essential in several patients affected by C3G, but the usefulness of such a blockade should be weighed against potential drawbacks as the block of C3b with its critical role in innate immunity.

To date, there are essentially 3 drugs aimed to exert a blockade at the C3 level. The compstatin analog Cp40 was documented to be effective in inhibiting complement dysregulation *in vitro* in C3G[114]. Compstatin binds to C3 and C3b, preventing the complement dysregulation caused by genetic mutations or by auto-antibodies. To date, compstatin is used in trials for macular degeneration and PNH. Similarly, a monoclonal antibody, which inhibits C3 convertase induced by C3NeF by binding to C3b is currently in the preclinical phase[115]. The most advanced drug among the C3 inhibitors is CDX1135, which is also known as TP10 and the soluble complement receptor 1 (sCR1). CR1 is a cell surface glycoprotein expressed on several cells, including immune cells. sCR1 is a protein that can regulate C3 convertase. Under normal conditions, only small quantities of sCR1 are in circulation. Administration of a high quantity of sCR1 in patients undergoing cardiac surgery revealed that this protein is able to exert a complement inhibition effective and safe[116,117]. Recently, at Iowa University, the efficacy of sCR1 has been documented in vitro and in mice affected by C3G[118].

Renal transplantation: C3G has a frequent evolution towards ESRD. Renal transplantation has been proposed for ESRD patients affected by C3G. Renal transplantation in such patients has two principal challenges: (1) whether to perform a dual liver-kidney transplantation; and (2) The high recurrence rates of the disease and its treatment.

The question of liver-kidney transplantation has

been previously mentioned above[86-88] and has been documented that in the eculizumab era, the liver-kidney transplantation will lose its relevance.

In the case of the kidney transplant alone the principal challenge is the high recurrence rate. In the case of DDD, the risk of recurrence is over 70%[119], with a high risk of graft loss[120,121]. These data confirmed a retrospective United States study including 75 children affected by DDD[122] and a more recent Irish cohort, including 33 patients affected by DDD[123]. Fewer data have been reported on the recurrence risk of C3GN. The most relevant study has been published by Zand *et al*[124] from the Mayo clinic. They report 21 renal transplant patients affected by C3GN. The recurrence rate was as high as 70% and the graft failure occurred in 50% of the patients. Importantly, all these reports with high recurrence rates also include patients transplanted in the pre anti-complement era. Transplants in patients affected by CFHR nephropathy has been reported in 11 subjects. All transplants were successful, despite the histological recurrence in three patients[125].

The treatment of recurrent disease has not yet been the object of clinical trials. Close monitoring is mandatory following renal transplantation to promptly detect the clinical signs of recurrence. Patients with circulating auto-antibodies might be treated by agents targeting T and B cells, but we should remember that the transplanted patients are already on immunosuppressant drugs.

Anti-complement drugs are promising. McCaughan *et al*[93] described the first report of a transplanted patient affected by recurrent DDD and who was successfully treated by eculizumab. However, the long-term dependence on eculizumab and the long-term safety of the drug remain open questions and the object of future RCTs. Another interesting approach is the use of sCR1, but its use to date has been limited to the native disease and not to its recurrence after transplantation.

Clinical trials ongoing: C3G is a rare disease and it is not surprising that ongoing RCTs are scarce. From one perspective the market interest is poor due to the few numbers of patients. However, a wide comprehensive multinational network among centers should be developed to include a significant number of patients for a RCT.

To date, four clinical trials are ongoing on C3G. Two trials aimed to evaluate eculizumab therapy in DDD and C3GN[100,126]. Two other RCTs are evaluating the effect of two different formulations of sCR1 on C3G[127,128].

Other drugs, such as compstatin and monoclonal antibody against C3 convertase, are still in the pre-clinical phase.

CONCLUSION

The Mayo Clinic/Renal Pathology Society Consensus Conference held in 2015 allowed the elaboration of a new etiology-pathology based classification of the GN, which substitutes for the old morphologic-based classification (1). In addition, before the Consensus Conference, the

MPGNs had been the object of new classifications for several years. To date, it is clear that the MPGNs should be distinguished into two principal categories: The immune-complex-mediated MPGN and the complement-dysregulation-mediated MPGN. This finding is principally relevant, not only from a taxonomic perspective, but also from a diagnostic and therapeutic approach. New findings in the complement related pathways and in genetics allowed for an improved understanding and definition of complement related MPGN, in addition to the discovery of new entities, such as C3GN and CFHR5 GN. To date, the MPGNs have a new diagnostic approach with a new network that applies to the immune-complexes related MPGN and complement-related MPGN.

Currently, fewer new drugs are available for the treatment of immune-complexes MPGN.

With the discovery of complement-inhibitor drugs, there has been more progress for the complement related MPGN. However, due to the rarity of the disease, well conducted RCTs are scarce. This finding supports the need to perform more multinational cooperative studies to identify an evidence-based medicine therapeutic approach.

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