C3 glomerulopathy disease

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SUMMARY
C3 glomerulopathy is a recently defined disease that encompasses a group of kidney diseases caused by abnormal control of complement activation. C3G is characterized by deposition of dominant complement C3 with absence/traces of immunoglobulins in the glomeruli. C3G may be classified into dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). DDD and C3GN are rare forms of glomerulonephritis that affect both children and adults. In treatment C3G include on specific treatment, plasma therapy, immunosuppressive and complement inhibition.

Keywords: C3 glomerulopathy, C3 glomerulonephritis, dense deposit disease, complement disorder

INTRODUCTION
C3 glomerulopathy (C3G) is a rare renal disease associated with the complement. The frequency of occurrence is two per million people¹. Both genders are equal. Although it can be seen at any age, it is more common in childhood and young adults. C3G is divided into two in itself as C3 glomerulonephritis (C3GN) and Dens Deposit Disease (DDD)². DDD has an estimated prevalence of 2 to 3 per million populations³. In a study conducted, 5-year renal biopsy results were evaluated and C3G was detected in 0.7% of them. In this study, DDD and C3GN were found at an equal rate. When DDD patients were compared with C3GN patients they were found to be younger. Also in study, C3G was found more frequently in men⁴. Differential diagnosis between DDD and C3 GN is necessary. Also, glomerular disease caused by mechanisms other than alternative complement dysregulation may occasionally satisfy “C3-dominant deposition with scanty immunoglobulins” as stated in the current consensus report⁵. Pathogenesis-based classification in glomerular disease is an important prospect for appropriate therapies, but the entity of C3 GN still presents dilemmas in diagnostic and pathogenetic basis. The aim of this review was to understand of the specific pathophysiology of this disease and ordering logical therapies.
PATHOGENESIS AND CLINICAL FEATURES

C3G immunofluorescence (IF) or immunohistochemical (IHC) methods are characterized with C3 dominant accumulation in glomerular and C3 dominant accumulation in glomerular and no or minimal immunoglobulin accumulations. The most common patterns in light microscopy (IM) in C3G may include membranoproliferative glomerulonephritis (MPGN), diffuse proliferative glomerulonephritis, mesangial proliferative glomerulonephritis and even necrotizing and crescentic glomerulonephritis. Rarely, glomerular can be normal with IM. Subendothelial intramembranous associated with wear of lamina densa and glomerular basement membrane thickening together with various combinations of subepithelial deposits and mesangial cell proliferation increase can be observed. At the same time, C3GN may show large subepithelial hump like deposits defined for DDD. In light microscopy, DDD is mostly found in mesangial proliferation. Significant endocapillary proliferation, leukocyte infiltration and crescent can be seen. In both diseases, predominant C3 stained with IHC, so EM is required for discrimination of both diseases. In C3GN, discrete C3 deposits are located in the mesangium and along the capillary wall, whereas in DDD C3 deposits are more intense and located in the mesangium and within the glomerular basement membranes.

In MPGN IF staining, if there is positive immunoglobulin ± C3 staining, it is divided into as glomerulonephritis associated with immunoglobulin (monoclonal gammopathy, autoimmune diseases, infectious diseases), if there is negative immunoglobulin and positive C3 staining, it is divided into as complement associated glomerulonephritis (DDD and C3GN). Besides C3G, there are different diseases showing dominant C3 accumulation with IF staining. Among these, post infectious glomerulonephritis (PIGN), infectious diseases (such as infective endocarditis), autoimmune diseases and paraproteinemina related diseases.

In cases of PIGN, there may be isolated staining for C3 on IHC/IF. Therefore, the distinction between PIGN and C3GN is required. PIGN is an immune complex-mediated glomerular injury. In a study conducted, an abnormality (acquired autoantibodies and genetic mutations) was found in the AP complement pathway in 11 PIGN patients. This is called atypical PIGN. However, when evaluating the data, most of these patients are classified as C3GN. In PIGN patients, there is a rapid recovery at renal function, haematuria, proteinuria and the level of the complement. In patients followed as PIGN, 8 weeks long hypocomplementemia, >500mg proteinuria contin one year later after diagnosis and/or if there is a progressive decrease in renal function, alternate complement path must be investigated and can be renamed as C3G. C3G is distinct from atypical hemolytic uremic syndrome (aHUS) although both diseases are due to abnormal control of the alternative pathway. (e.g.; abnormalities in CFH result in uncontrolled activation of C3 through the AP and associate with susceptibility to both C3G and aHUS). C3G and aHUS are rarely seen together. In aHUS, complement activation occurs on the glomerular or microvascular endothelium. Electron dense deposits on EM is not seen in most cases. Also glomerular C3 is not detected on IHC / IF. The minimum set of genes (CFH, CD46, CFI, C3, CFB, THBD, CFHR1, CFHR5, and DGKE) should be screened. In a patient with aHUS, the identification of a pathogenic genetic variant strengthens the diagnosis and initiates with accuracy the cause of the disease, facilitating patient management, effective treatment, and genetic counseling. But despite that in C3G, existing knowledge is inadequate except in cases of CFHR rearrangements leading to fusion genes (such as CFHR5 nephropathy), FH or FI deficiency, or with C3 mutations. Initial clinical manifestations of DDD and C3GN may be preceded by upper respiratory tract infection. Streptococcal infection C3G among infections is the most common triggering factor. Clinically, renal involvement of both patients is similar and nonspecific. Haematuria, hypertension, proteinuria, nephritic syndrome, nephrotic syndrome and renal insufficiency are defined. It may be accompanied by partial lipodystrophy in DDD patients. Retinal complications (such as drusen and atrophy) are commonly in C3G patients. Eye findings have previously been defined for DDD. Retinal drusen or whitish-yellow subepithelial deposits evident on fundoscopy have also been described in patients with DDD or C3GN. Drusen affect vision, initially only mildly but severely in the longer term.

C3G alternative complement pathway should be assessed. Serological complement assays may be informative in these patients. Serum membrane attack complex, complement C3 and C4 level should be observed. Besides, observing of CFH, paraprotein and C3NeF is recommended. Specific
activation of alternative complement pathway may characterize with low C3, low factor B and normal C4 level, increased degradation C3 products, low C5 and increased solubility C5b-9 and C5a levels. But these anomalies can change during the course of the disease. CFB deficiency may be associated with activation of uncontrolled alternative complement pathway. In the absence of CFH it is associated with C3G. Low level of complicated C3 supports C3G. Complement C4 is usually at the normal value. Acquired antibodies should be observed (C3NeF, CFH autoantibody, CFB autoantibody) and genetic mutations can be made (C3, CFH, CFI, CFB, MCP and CFHR)\(^5,10\).

Complement is part of the innate immune system and is composed of over 30 proteins. The complement system can be activated in 3 different ways. These are known as the classical pathway, the mannose-binding lectin pathway and the alternative complement pathway. The alternative complement pathway is different from others because of spontaneous active \(^15\). Overactivation of the alternative complement pathway by autoantibodies or mutations or as a result of regulatory defect C3G can develop. Complement C3 deposition in the renal and systemic C3 consumption are hallmark feature of C3G. C3NeF, anti-complement factor H, anti-complement factor I, anti-complement factor B, anti-C3b were determined among autoantibodies. CFH, CFB, CFI, MCP, complement C3, CFHR 5, CFHR3-1 were determined among complement mutations\(^16-18\). In a study of 134 patients with DDD, C3GN and MPGN type I diseases, alternative complement pathway hereditary or acquired complicated impairment was detected in \(71\%\). C3NeF is the first defined autoantibody. The C3 connects and stabilizes the converter. In this study, 86.4\% of C3NeF DDD patients and 45.3\% of C3GN patients were detected \(^19\).

Familial C3G are five complement factor H-related genes: CFHR1, CFHR2, CFHR3, CFHR4, and CFHR5. CFHR5 nephropathy is C3GN subtype. In Cyprus, CFHR5 nephropathy is a hereditary renal disease. It usually develops after upper respiratory tract. Clinically, persistent microscopic haematuria, synphryngitic macroscopic hematuria and renal dysfunction characterize CFHR5 nephropathy. There is CFHR5 mutation. CFHR5 nephropathy is autosomal dominant. With progression to end stage renal failure (ESRD) is common lately, renal transplant is successful in these patients\(^5,20-21\). The \(CFHR3-1\) gene is cause of atypical hemolytic uremic syndrome and C3G. The \(CFHR3-1\) gene is also common in healthy populations\(^22\).

In studies evaluating the prognosis of C3G; 10-year renal survival was lower than 50% and after 28 months of follow-up, the rate of ESRD development rate was found as 29\% (a total of 21 DDD patients and 59 C3GN patients were included in this study) \(^23\). In another study, 10-year renal survival (a total of 29 DDD patients, 49 type I MPGN patients and 56 C3GN patient were included in this study) was 63.5\% of the patients after diagnosis ESRD develops. Also in this study, the prognosis of DDD patients is reported to be worse than the other two diseases \(^19\). Being patients older than 16 years old, having DDD, crescentic glomerulonephritis, renal dysfunction, having IM MPGN pattern detection is considered as a high risk for progression of ESRD \(^19,23\).

**TREATMENT**

C3G treatment is in the form of nonspecific treatment, immunosuppressive treatments, plasma treatment, inhibition of complement activation and renal transplantation. Nonspecific treatment, blood pressure control, reduction of proteinuria and reduction of serum lipid level has beneficial effects on the progression of C3G. Angiotensin receptor blockers and angiotensin converting enzyme inhibitors are used in proteinuric renal diseases as antihypertensive and antiproteinuric. Their use has been associated with better survival in patients with MPGN. Antiproteinuric antihypertensives are recommended in patients with C3G \(^19,24\). According to expert opinion of Kidney Disease Improving Global Outcomes” (KDIGO); optimal blood pressure control (Priority agents include angiotensin converting enzyme inhibitors and angiotensin receptor blockers) and lipid control are recommended in all patients\(^12\).

Due to lack of immunosuppressive therapy controlled studies in treatment of C3G, severe inflammation findings, progressive glomerular filtration loss in renal biopsy and/or its use in patients with proteinuria is limited. McCaughan reported a failure to respond to glucocorticoid, mycophenolate mofetil and rituximab therapy \(^25\). Bombac et al. showed treatment failure of the use of prednisolone and mycophenolate mofetil in a C3GN \(^26\). On the contrary, clinical improvement in many in acute glomerulonephritis cases containing crescent with steroid therapy has been reported during C3G pediatric series \(^27\). Moderate disease (over 500 mg/24h of urine protein or moderate inflammation on renal biopsy or a risk of progressive disease) according to KDIGO; prednisolone and mycophenolate mofetil are recommended for treatment. Severe disease (over
2000 mg/24h of urine protein or Severe inflammation represented by marked endo- or extracapillary proliferation with or without crescent formation on renal biopsy or a risk of progressive disease despite immunosuppression and supportive therapy) according to KDIGO. In patients with rapid progressive renal disease, methylprednisolone pulse dosing or other anti-cellular immunosuppressants have had limited success and data are insufficient to recommend eculizumab as a first-line agent. DDD-associated anti-Cfb / C3b autoantibody was reported that in a case treated successfully with rituximab. In a study by Robosco et al they have shown that immunosuppressive therapy was particularly effective in the treatment of C3GN with mycophenolate mofetil therapy as an immunosuppressive adjunct. In addition, immunosuppressive treatment may possibly be predominantly effective in relation to autoantibody from C3GN forms. In patients with proven antibodies against complement regulatory protein, drugs like steroids, cytotoxic drugs and rituximab may be useful. In patients with crescentic GN, these drugs together with steroids may also have a role.

Although plasma exchange should theoretically be useful as it can remove autoantibodies and mutated proteins, it has met with only limited success. Licht et al. reported efficacy of plasma therapy in a sibling pair with DDD and a factor H deficiency secondary to a mutation in CFH. Both Banks and Krmar et al have reported that patients with acute renal failure and DDD were treated with plasma exchange, cyclophosphamide and methylprednisolone. McCaughan et al, on the other hand, did not respond to treatment plasmapheresis, steroids and rituximab in patients with recurrent DDD after renal transplant. This patient has been shown to recover after treatment with eculizumab. Kurtz et al. have shown that long-term plasmapheresis is effective and safe in a recurrent DDD patient. The level of C3NeF is reduced and serum creatinin are kept constant with plasmapheresis. In 4 C3GN patients with C3NeF detected (excluding all other known complement factor mutations) plasma therapy, corticosteroids and mycophenolate mofetil was found effective with regimen therapy. In a study of hemolytic uremic syndrome patients, MCP mutation patients were found to have better prognosis than patients without mutation and CFH, effect of plasma treatment on MCP mutations could not be shown (both plasma treatment and no plasma treatment improved the majority of patients). It was emphasized that the renal transplant outcomes were successful in these patients. When plasmapheresis or plasma exchange is given alone or with other medications, 85% in non-mutated, 94% in those with CFH mutations, 71% MCP mutation and 61% CFI mutation were found. CFH, CFI, C3 and CFB are produced by the liver. Concomitant liver transplantation together with kidney transplantation can be used effectively for them. Consequently, plasma therapy may be useful in patients with regulatory factor deficiency or with circulating C3NeF. Plasma infusion may replace the deficient factor. The frequency and duration of plasma therapy is unclear.

Cleavage of C5 is blocked by Eculizumab, consequently it blocks both formation of C5b-9 and the production of the anaphylatoxin C5a. Eculizumab is used in the treatment of Paroxysmal nocturnal hemoglobinuria and aHUS. For both diseases, eculizumab in adult is initially administered 600–900 mg intravenously weekly. Maintenance of treatment is administered 900–1200 mg/ 2 weeks. The main adverse effects are infusion reactions and infections, especially meningococcal infections. Before induction of eculizumab Meningococcal vaccination is required and until 2 weeks after vaccination prophylactic treatment with appropriate antibiotics should be preserved. There are case reports and small clinical trials that have demonstrated the efficacy of intravenous treatment with eculizumab. In the study C3G (3 DDD and 3 C3GN) of Bomback et al it found to be effective in the inhibition of terminal complex cascade of treatment with eculizumab. Besides, serum membrane attack complex height in patients may predict response to treatment with eculizumab. At the end of this study, it was emphasized that treatment with eculizumab might be suitable for C3G patients. Oosterveld et al showed that eculizumab treatment was successful in paediatric DDD (C3NeF in 3 patients, anti-CFH in one patient, CFHR1-CFHR3 mutation in one) patients. Also, two patients were discontinued dialysis treatment. All of the patients had well tolerated the treatment with eculizumab. In a DDD case showing nephrotic proteinuria, low C3, lack of CFH, CFH polymorphism and C3NeF antibody positivity, it has been found that eculizumab treatment is effective. In a case having C3GN diagnosis (CFHR1-CFHR3 mutation) Inman et al has presented a case of dialysis treatment discontinued 5 months after treatment with eculizumab. C3GN has been treated successfully in a few cases with eculizumab treatment.
Soluble Complement receptor 1 (sCR1) is complement C3 inhibitor (sCR1 is inhibits the complement activation cascades by binding both C3b and C4b). sCR1 prevented C3 convertase activity in normal and pathologic conditions. sCR1 also prevents dysregulation of the alternative pathway C3convertase in the presence of C3NeF and genetic mutations. As in vivo, C3G stopped the dysregulation of alternative complement pathway sCR1 in two mice and normalized plasma C3 levels. These changes were accompanied by reduced deposition of new iC3b and clearance of old iC3b in the glomerular basal membrane.

Cp40 complement is C3 inhibitor. Cp40 prevents formation of C5 convertase, production of C5a, soluble C5b-9 and lytic membrane attack complex. Cp40 extinguishes impaired complete disregulation by genetic mutations and autoantibodies such as C3NeF and C4NeF and prevents the lysis of complement-associated erythrocytes. It is seen as a specific treatment for the disease in C3G.

It has turned out that steroid therapy, eculizumab therapy, renal transplantation and liver transplant and CFH replacement are ineffective for drusen treatment. Laser therapy stabilizes vision in some cases of neovascularization. Also, recurrent bevacizumab and anti-VEGF injections may correct the sight in DDD patients.

Because C3G patients are usually children and young adults, the renal transplantation rate is high in these patients. Besides, renal transplantation provides good survival in patients with ESRD. However, Recurrent of disease in patients with C3G and graft loss rates are high. In carried out studies, transplantation recurrence rates as high as 66.7% of patients with C3GN and up to 70% of patients with DDD.

CONCLUSION

Consequently, more detailed laboratory and clinical data about the disease will be obtained after the new classification of C3G. In addition, more specific treatment modalities will emerge. Also, differential diagnosis of these diseases should be made from other with alternative complement pathway disorders. In the treatment of C3G, angiotensin receptor blockers and angiotensin converting enzyme inhibitors are recommended. C3G are conflicting results regarding treatment. More extensive and comprehensive research is needed for targeted treatments.

REFERENCES


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