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C3 glomerulopathy

ABSTRACT

C3 glomerulopathy (C3G) is a rare kidney disease that causes kidney dysfunction as a result of dysregulation of the complement system alternate pathway (AP). C3G encompasses 2 separate disorders, C3 glomerulonephritis and dense deposit disease. The presentation and natural history is variable and kidney biopsy is needed to confirm the diagnosis. The overall prognosis is poor with high recurrence rates after transplant. A better understanding of C3G is needed as is high-quality evidence to guide therapy, which currently includes mycophenolate mofetil and steroids for moderate to severe disease, and terminal complement blockade with anti-C5 therapy in unresponsive cases.

KEY POINTS

- C3G affects children and adults and is caused by dysregulation of the complement AP.
- Patients typically present with proteinuria and hematuria, ranging from asymptomatic urinary abnormalities to classic acute glomerulonephritis with kidney dysfunction and hypertension.
- Children and young adults usually present with urinary abnormalities following an upper respiratory tract infection.
- Progression to end-stage kidney disease occurs in up to 50% of patients in 10 years.

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INTRODUCTION

C3 glomerulopathy (C3G) is a group of rare diseases that cause kidney malfunction encompassing 2 entities that likely represent a continuum: C3 glomerulonephritis (C3GN) and dense deposit disease (DDD). These disorders are mediated by dysregulation of the complement system alternate pathway (AP) affecting children and adults. The term C3 glomerulopathy was adopted in 2013.[1] DDD has historically been known as membranoproliferative glomerulonephritis type II, but is now reclassified as complement-mediated membranoproliferative glomerulonephritis.

C3G has a variable clinical presentation. The prognosis is quite poor, with approximately 50% of adults progressing to end-stage kidney disease within 10 years of diagnosis.[1] C3G is notorious for recurrence after transplantation, with poor allograft survival rates. Better understanding of this disorder has recently been attained, paving the way for new therapeutic options.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

The incidence of C3G in the United States is estimated to be between 0.5 and 3 cases per 1 million, with a point prevalence ranging from 14 to 40 cases per 1 million.[1] DDD appears to be less common than C3GN and is usually diagnosed in childhood or early adulthood.[2,3] Patients usually present with proteinuria and hematuria ranging from asymptomatic urinary findings to the classic acute glomerulonephritis with kidney dysfunction and hypertension. Proteinuria can be subnephrotic or nephrotic, and kidney dysfunction can be acute with rapidly progressive glomerulonephritis or subacute. Children and young adults, unlike older adults, usually present with urinary abnormalities following an upper respiratory tract infection. The prognosis for patients with C3G is generally poor, worse for DDD than C3GN, with progression to end-stage kidney disease in up to 50% of patients in 10 years.[2]

Extrarenal manifestations include retinal drusen,[4] similar to those seen in age-related macular degeneration. Acquired partial lipodystrophy may be present,

mostly with DDD, in what is called the Dunnigan-Kobberling syndrome.[5] These patients present with fat loss in the upper part of the body sometimes years before C3G is diagnosed. As is the case with C3G, dysregulated complement activation in the retina and adipose tissue are thought to be the mediator of these extrarenal pathologies.

SEROLOGIC WORKUP AND DIAGNOSIS

The presentation of C3G is quite variable, with considerable overlap with other glomerular pathologies. It remains a histopathologic diagnosis hinging on immunofluorescence and electron microscopy for subcategorization.[1] Serologic workup reveals low C3 levels in around two-thirds of patients with C3G (75% of DDD; 50% of C3GN). Adults are less likely to present with low C3.

Kidney biopsy reveals granular to semilinear deposits that are C3 dominant, at least 2 orders of magnitude greater intensity than other immunoreactants. Subclassification of C3G to C3GN or DDD requires electron microscopy, which in DDD would highlight "sausage-shaped," intensely electron-dense, osmiophilic deposits within the lamina densa of the glomerular basement membrane. Electron microscopy in C3GN shows lower intensity (or less intense) electron-dense, hump-like deposits in the mesangium, subendothelial, and sometimes subepithelial spaces. Mass spectroscopy of these deposits can reveal components of the AP.[1,3] It is noteworthy that classic subepithelial humps identical to those seen in post-streptococcal glomerulonephritis can be seen in both DDD and C3GN, making pathologic distinction between these entities impossible.

While immunofluorescence and electron microscopy are diagnostic of C3G, light microscopy findings are highly variable, showing mesangial hypercellularity, membranoproliferative, endocapillary proliferative, sclerosing, or more rarely, exudative and crescentic patterns.[1,3] Patterns seen on light microscopy can suggest disease severity, predict prognosis, and provide guidance in terms of the need for immunomodulatory therapy.

When dealing with a C3-dominant kidney process, an infection-related glomerulonephritis must be excluded. While most cases of infection-related glomerulonephritis are immune complex-mediated, showing immunoglobulin (Ig) M, IgG, or IgA positivity in addition to C3, some cases can be C3 dominant. In such cases, it is indistinguishable from C3G pathologically, and an infectious process should be excluded. Persistent or worsening kidney dysfunction after resolution of an infectious process with persistent low C3 should raise the suspicion for C3G, with consideration for repeat kidney biopsy after 12 weeks to exclude C3G.

PATHOGENESIS AND EVALUATION

C3G is driven by dysregulation and excessive activation of the AP resulting in deposition of complement components in the glomerulus.

The AP is constitutively active with a low-level spontaneous hydrolysis of C3. This leads to the formation of C3 convertase (C3bBb), which then leads to robust amplification of the complement response, cleaving more C3 and ultimately generating the C5 convertase (C3BbC3b). These convertases cleave C5 into C5a, a powerful anaphylatoxin, and C5b, which initiates assembly of C5b-9, the membrane attack complex. Activation of the AP is tightly controlled via regulators of complement activation, mainly factor H, which facilitates the decay of the active C3 and C5 convertases. Other regulators of complement activation include factor I- and factor H-related protein as well as membrane cofactor protein, complement receptor 1, and decay-accelerating factor.[1]

AP dysregulation results from genetic or acquired factors. Genetic factors are involved in around 25% of patients with C3G, mainly in C3 and factor B proteins,[6] rendering the active convertases resistant to hydrolysis. More commonly, AP dysregulation results from autoantibodies to various complement proteins. The most common autoantibody is C3 nephritic factor, which stabilizes C3 convertase. Autoantibodies are present in up to 80% of patients with DDD and 50% of patients C3GN.[7] C5 nephritic factors are also common, stabilizing the C5 convertase with ongoing AP activation.

Patients diagnosed with C3G should have a complete evaluation for complement abnormalities, including levels of factors H, B, and I, membrane cofactor protein, and soluble membrane attack complex. Complement-directed antibodies should be checked, in addition to a complete genetic evaluation of the AP components. Some specialized laboratories offer panels, such as Cincinnati Children's Hospital Medical Center and Mayo Clinic. Identifying the driving pathology can have important clinical and therapeutic implications.

A monoclonal gammopathy should be tested for in all adults with C3G. Although the paraprotein may not be evident on the kidney biopsy, it may target regulatory elements of the AP leading to complement

activation and C3G. Treatment should be directed toward eliminating the hematologic clone.[8]

TREATMENT

Nonimmunomodulatory therapy

There currently is no uniform therapy for C3G, but several compounds in clinical trials are showing promise. Currently, patients with relatively mild disease (preserved kidney function and proteinuria less than 1.5 g per 24 hours) should be managed with nonimmunomodulatory therapy. Unless a contraindication exists, all patients with C3G should receive antiproteinuric therapy by inhibiting the renin-angiotensin system. This is consistent with the 2021 Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[9] Interestingly, renin has been shown to facilitate the enzymatic cleavage of C3 to activate the AP. Aliskirin, a renin inhibitor, was shown to modulate that effect[10] and is now being investigated compared with enalapril in an ongoing clinical trial. Other conservative measures include dietary sodium and animal protein restriction, blood pressure management, and cholesterol management. Sodium-glucose cotransporter inhibitors have become a pillar of conservative anti-proteinuric therapy in patients with glomerular diseases. Although data are wanting in C3G, unless a contraindication exists, these agents should be utilized.

Nonspecific immunomodulatory therapy

Patients with moderate to severe disease should be considered for treatment with immunomodulatory therapy. The KDIGO guidelines suggest initial therapy with mycophenolate mofetil (MMF) plus glucocorticoids in these patients.[9] This is based on observational studies showing higher rates of remission in patients treated with MMF plus steroids than with other forms of immunosuppression. Remission rates with MMF ranged between 36% and 65%, with around one-third of patients relapsing after therapy discontinuation.[11,12] Patients who had positive C3 nephritic factors appeared to respond better to MMF therapy. Given the lack of high-grade evidence to guide therapy, we encourage patients to enroll in clinical trials.

Plasma exchange or infusion is another immunomodulatory therapy used in patients with C3G. Robust data are lacking, with supporting evidence coming from case reports. Positive outcomes were reported only in patients with factor H abnormalities (genetic variant or an acquired deficiency).[13] It is the infusion of healthy factor H, as opposed to antibody removal, that is thought to be helping these patients. The use of plasma exchange is reserved for severe cases (with factor H pathology) not responding to initial treatment. No data exist to guide the duration of therapy. If patients respond, therapy could be chronic.

Specific anticomplement therapy

The KDIGO guidelines suggest terminal complement blockade with eculizumab (anti-C5 monoclonal antibody) in patients who fail to respond to MMF.[9] Failure to respond is indicated by worsening kidney function or proteinuria or both. Data for this strategy are not robust, with less than 50% of patients responding to eculizumab.[14] Le Quintrec et al found that patients presenting with lower glomerular filtration rate, more rapidly progressive disease, and more extracapillary proliferation were more likely to respond. This modest efficacy has been hypothesized to be related to the fact that eculizumab fails to impact upstream C3 dysregulation[1] Multiple agents targeting upstream elements of the AP are currently in advanced clinical trials with encouraging preliminary data. These include a factor B inhibitor (iptacopan),[15] factor D inhibitor (danicopan),[16] and a C3 inhibitor (pegcetacoplan). An oral C5a receptor 1 inhibitor (avacopan) is also in clinical trials. Currently, patients not responding to initial therapy or having severe disease are recommended anti-C5 therapy, but we favor enrolling these patients in available clinical trials. Meningococcal vaccination is imperative for patients treated with anti-C5 therapy, ideally 2 weeks before the first dose. Fatal meningococcal infections have been reported.[17] We also suggest long-term daily antimicrobial prophylaxis.

CONCLUSION

C3G is a rare kidney disease resulting from dysregulated AP. Presentation is quite variable and kidney biopsy is necessary to confirm the diagnosis. Natural history varies, with an overall poor prognosis and high rates of recurrence after transplant. High-quality evidence is lacking, but therapy with MMF and steroids is currently recommended for moderate to severe disease. Terminal complement blockade with anti-C5 therapy is reserved for unresponsive cases, with modest efficacy. Multiple trials of proximal complement blockade are ongoing. It is highly likely that C3G is more than a single disease entity. As we better stratify and understand our patients based on complement activity and underlying genetic predispositions, and as new drugs become available, we hope to be able to provide better personalized care for our patients.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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