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C3 Glomerulonephritis versus “C3 Glomerulopathies?”

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Background and epidemiology

C3 glomerulonephritis (C3Gn) is a due to abnormal regulation of the alternative complement pathway. The diagnosis is based upon kidney biopsy immunofluorescences studies showing isolated or dominant C3 deposition within the glomerulus with little or no immunoglobulin deposition.[1] It is a distinct entity from the other 4 classes of glomerulonephritis (Gn): immune complex, pauci-immune, antiglomerular basement membrane antibody, and monoclonal Gn.[2] One caveat to immune complex disease is that there is a subset of patients with atypical post infectious glomerulonephritis who have persistent lab abnormalities (low C3, proteinuria, or elevated creatinine). Patients with an atypical post infectious course may have C3Gn.

The cause of C3Gn is excessive activation of the alternative complement pathway. The primary defect is increased activity of the C3 and C5 convertases.[3] One mechanism underlying the increased activity of these convertases is the development of a stabilizing autoantibody called C3 nephritic factor (C3NF). Indeed, C3 nephritic factor hinders the breakdown of C3 convertase, allowing it to continue to amplify the cascade resulting in increased production of C3 and by also generating the C5 convertase which itself initiates the membrane attack complex.[4] The other mechanism responsible for increased activity of the C3 convertase is the loss of factor H functionality. Since the normal function of factor H is to inhibit the C3 convertase, mutations or acquired loss of the ability of factor H to regulate activated C3 results in excessive convergence towards assembly of the membrane attack complex.[4]

C3 glomerulonephritis is a pediatric disease and rates of diagnosis are increasing with greater awareness of this distinct and separate entity from dense deposit disease (DDD), both of which are commonly classified under the broad heading of C3 glomerulopathies (Table 1).[3,5,6] Unfortunately, the classification of both C3Gn and DDD as C3 glomerulopathies adds confusion to the classification schema due to subtleties in the nomenclature.

Table 1. C3 Glomerulopathies: Comparing and Contrasting Dense Deposit Disease versus C3 Glomerulonephritis.

Descriptive Factor	Dense Deposit Disease	C3 Glomerulonephritis
Pathophysiology	Abnormal regulation of the alternative complement pathway	Abnormal regulation of the alternative complement pathway
Light microscopy findings	Almost always a membranoproliferative glomerulonephritis pattern	Any pattern
Immunofluorescence findings	Dominant C3 staining	Dominant C3 staining
Electron microscopy	Linear electron dense material within in the glomerular basement membrane (intramembranous) Dense deposits	Subendothelial, subepithelial and/or mesangial electron-dense deposits ; Lighter density deposits
Age of affected	Children and young adults; over half will be < 16 years of age at diagnosis.	Children and young adults; about a quarter will be < 16 years of age at diagnosis.
C3 nephritic factor	Present 80% of the time	Present 40% of the time
Serum C3 level	>80% have low C3 levels	Approx. 50% have low C3 levels
Soluble C5b-9 level	Elevated in 9%	Elevated in 50%
Pathological gene variant	Identified in 25%	Identified in 25%
Dysregulation of alternative	Favors dysregulation of the	Favors dysregulation of the

pathway convertase	C3 convertase	C5 convertase
Extrarenal abnormalities	Drusen deposition in Bruch's membrane of the retina (macular deposits)	
Risk of end stage kidney disease (ESKD)	Approx. 70% progress to ESKD	Approx. 35% progress to ESKD
Risk of recurrence after kidney transplant	>50% (100% in some studies)	>50%

Presentation

The presentation of C3Gn is variable, but urine abnormalities are always present. Most patients with C3Gn present with nephrotic range proteinuria and/or nephrotic syndrome and hematuria. Cases presenting with subnephrotic range proteinuria or isolated gross hematuria have been reported. The clinician cannot use serum C3 levels or other blood work as a discerning factor from other forms of GN.[3] Therefore, a kidney biopsy is required to establish the diagnosis.[5] Although most biopsies of C3Gn show a membranoproliferative pattern, this is not required. Immunofluorescence (IF) must show dominant C3 glomerular staining in the mesangium and capillary loops that is at least 2+ stronger than other IF stains.[2] Electron microscopy helps differentiate from DDD with C3Gn, with the latter showing lighter mesangial, subendothelial, or epithelial deposits rather than intramembranous linear dense deposits diagnostic of DDD.

Diagnosis and Patient Management

C3Gn is a rare disease with an incidence of 1-2 million/year (Table 2).[5] Therefore, due to lack of clinical experience, a standard causative work up/approach cannot be recommended. However, based upon our current understanding of the pathophysiology (over activity of the

alternative complement pathway) evaluation may require genetic testing for mutations in alternative complement proteins and measurement of autoantibodies (Table 3).[3,7]

Table 2. Incidence of Pediatric Nephrology Conditions

Disease/Condition	Incidence
C3 Glomerulonephritis	**1-2 per million**
Dense Deposit Disease	**1-2 per million**
Autosomal Dominant Polycystic Kidney Disease	1 per 1,000
Autosomal Recessive Polycystic Kidney Disease	1 per 40,000
Immunoglobulin A Nephropathy	3 per 100,000
Nephrotic Syndrome	4 per 100,000
Pediatric End Stage Kidney Disease	10 per million
Posterior Urethral Valves	1 per 10,000

Table 3. Considerations for the Cause of C3 Glomerulonephritis

Genetic Mutations	*C3, CD46 (membrane cofactor protein), CFB, CFH, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5, CFI*
Autoantibodies	C3 nephritic factor (anti-complement factor C3bBb), anti-complement factor H, anti-complement factor B, anti-complement factor C3b

A standard and effective treatment is not available (Table 4). A coherent argument can be made for targeting autoantibody (C3NF) generation and/or utilizing drugs and procedures (such

as therapeutic plasma exchange) that dampen the alternative pathway activity.[5,6] Assessing the efficacy of any one therapy is difficult due to the inclusion of patients with membranoproliferative glomerulonephritis type 1 (which includes both C3 glomerulonephritis and immunoglobulin and immune complex glomerulonephritis) in many studies.[5] Further, reports of efficacy from single/small case series show promising results but are subject to publication bias with the non-responders never reported.

Table 4. Considerations for the Treatment of C3 Glomerulopathies: Dense Deposit Disease versus C3 Glomerulonephritis.

Therapy	Dense Deposit Disease	C3 Glomerulonephritis
Glucocorticoids	No benefit	Possible benefit
Eculizumab	Possible benefit	Possible benefit
Plasma Exchange	Possible benefit	Possible benefit
Plasma Infusion	Possible benefit	No experience reported
Calcinuerin Inhibitors	No benefit	Possible benefit
Mycophenolate Mofetil	No benefit	Possible benefit
Rituximab	No benefit	Possible benefit

Greater awareness of this “new” disease entity will facilitate diagnosis and potential enrollment in study registries and prospective studies evaluating differentiating clinical parameters and therapies. Due to the rareness of C3Gn, this approach will be necessary to help inform best clinical practice.

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