PATHOPHYSIOLOGY AND DIAGNOSIS OF COMPLEMENT 3 GLOMERULOPATHY (C3G)

C3G IS A COMPLEX, CHRONIC, RARE GLOMERULAR CMKD[1]

- Characterized by **overactivation of the AP** and **C3 deposition** in the kidney[1-3]
- Includes two subtypes: DDD and C3GN[1]
- Causes progressive renal failure and is associated with emotional/societal difficulties that affect patients' quality of life[4,5]

Estimated annual US incidence:

2-3 cases per million[1,6]

Affects individuals of all ages

starting early in childhood and young adulthood[7]

Incidence rates are similar in men and women[8]

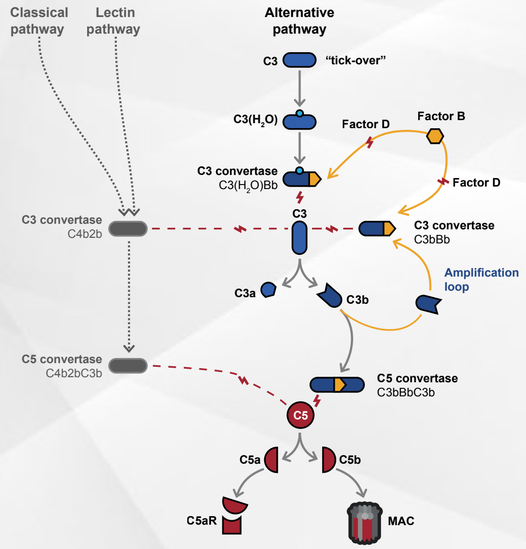
1:1

CLINICAL PRESENTATION OF C3G IS HETEROGENEOUS[2,9-11]

- Ranges in **severity** from asymptomatic hematuria and proteinuria, or nephritic and nephrotic syndrome, to rapidly progressive glomerulonephritis with acute kidney injury[2,9,10]
  - Other common clinical manifestations include fatigue, edema, and hypertension[4]
  - **Extra-kidney symptoms** have been reported, such as acquired partial lipodystrophy found in 5% to 17% of patients and ocular complications (drusen) in ~10% of patients, potentially causing vision loss in later life[10]
- **Can be stable for years** despite persistent proteinuria, although **rapid fluctuations** with episodes of **acute kidney deterioration can occur in some patients**[10]

DYSREGULATION OF THE AP IS THE MAIN DRIVER OF THE PATHOGENESIS OF C3G, LEADING TO THE DEPOSITION OF C3 IN THE GLOMERULI[1-3,9]

- C3 accumulation causes glomerular inflammation and injury, leading to proteinuria, hematuria, chronic kidney disease, and potential kidney failure[1-3,9]
- The pathogenesis of C3G may be driven by genetic abnormalities in complement genes, autoantibodies against complement components, or nephritic factors that stabilize C3 and/or C5 convertases[2]
  - **AP dysregulation** occurs in >90% of patients with C3G[1]
  - **Genetic abnormalities** occur in ~25% of patients with C3G and mainly affect genes encoding C3, FB, FH, FI, and FHR[2]



Adapted with permission from Rizk et al.[13]

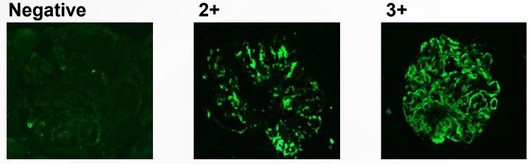
As C3G can be characterized by inherent genetic and acquired dysregulation of the AP, these abnormalities often remain after transplantation[12]

A KIDNEY BIOPSY IS THE ONLY WAY TO DIAGNOSE C3G[1]

- **Heterogeneous presentation of C3G and its similar presentation to other kidney disorders create challenges in differential diagnosis**[9,10]
  - An experienced renal pathologist is needed to interpret the biopsy findings using different imaging techniques
- **Diagnosis is exclusively made based on histological findings with IF and EM** and is dependent on the interpretation of individual cases through the integration of medical information by the kidney biopsy together with clinical, serological, and genetic assessments. Diagnosis requires[10,11]:
  - Initial laboratory testing
  - **Confirmatory biopsy with IF staining**
  - Further assessment of complement activity
- EM is needed to differentiate DDD and C3GN

C3 staining is at least two orders of magnitude greater than any other immune component, with absence or low presence of immunoglobulin and components of the classical complement pathway[3,10]

Examples of glomerular C3c staining by IF



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30% TO 50% OF PATIENTS MAY DEVELOP KIDNEY FAILURE WITHIN 10 YEARS OF DIAGNOSIS AND REQUIRE DIALYSIS OR KIDNEY TRANSPLANT[9,15]

- A retrospective study in the UK observed an **annual eGFR decline** of 4.9 mL/min/1.73m^2 per year in patients with C3G[16]
  - This RaDaR-MPGN analysis included 135 patients with biopsy-proven C3G. The inclusion criteria for the study may have led to enrollment of patients with more progressive disease and thus may represent a higher risk population. Reporting of proteinuria and eGFR data at disease onset was incomplete and may not be representative of the full cohort; however, data are likely to be missing at random with limited bias
- Posttransplantation recurrence and allograft loss is high (50% and 75% in DDD and C3GN, respectively)[7]
- DDD is more likely than C3GN to progress to kidney failure, although cumulative native kidney survival is similar[7]

AP, alternative complement pathway; C, complement; C3G, complement 3 glomerulopathy; C3GN, complement 3 glomerulonephritis; CKD, chronic kidney disease; CMKD, complement-mediated kidney disease; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; EM, electron microscopy; FB, factor B; FH, factor H; FHR, factor H-related protein; FI, factor I; IF, immunofluorescence.

1. Smith RJH et al. *Nat Rev Nephrol*. 2019;15(3):129-143. doi:10.1038/s41581-018-0107-2 2. Caravaca-Fontán F, Lucientes L, Cavero T, Praga M. *Nephron*. 2020;144(6):272-280. doi:10.1159/000507254 3. Schena FP, Esposito P, Rossini M. *Int J Mol Sci*. 2020;21(2):525. doi:10.3390/ijms21020525 4. National Kidney Foundation. Complement 3 glomerulopathy (C3G): knowing the signs and symptoms. Accessed April 22, 2024. https://www.kidney .org/atoz/content/complement-3-glomerulopathy-c3g-knowing-signs-and-symptoms 5. National Kidney Foundation. Externally led patient-focused drug development meeting: C3 glomerulopathy (C3G). The Voice of the Patient. March 26, 2018. Accessed March 2024. https://www.kidney.org/sites/default/files/C3G_EL-PFDD_VoP-Report_3-29-18.pdf 6. Bomback AS et al. *Kidney Int*. 2018;93(4):977-985. doi:10.1016/j.kint.2017.10.022 7. Medjeral-Thomas NR et al. *Clin J Am Soc Nephrol*. 2014;9(1):46-53. doi:10.2215/CJN.04700513 8. National Library of Medicine. C3 glomerulopathy. MedlinePlus. December 1, 2015. Accessed March 2024. https://ghr.nlm.nih.gov/condition/c3-glomerulopathy 9. Ahmad SB, Bomback AS. *Adv Chronic Kidney Dis*. 2020;27(2):104-110. doi:10.1053/j.ackd.2019.12.003 10. Martin B, Smith RJH. C3 glomerulopathy. In: Adam MP, Mirzaa GM, Pagon RA et al, eds. *GeneReviews®*. Seattle, WA: University of Washington; 2007 [updated April 5, 2018]. 11. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int*. 2021;100(4S):S1-S276. doi:10.1016/j.kint.2021.05.021 12. Salvadori M, Bertoni E. *World J Transplant*. 2016;6(4):632-645. doi:10.5500/wjt.v6.i4.632 13. Rizk DV et al. *Kidney Int Rep*. 2023;8(5):968-979. doi:10.1016/j.ekir.2023.01.041 14. Snijders MLH et al. *Mod Pathol*. 2020;33(3):431-439. doi:10.1038/s41379- 019-0348-z 15. Servais A et al. *Kidney Int*. 2012;82(4):454-464. doi:10.1038/ki.2012.63 16. Downward L et al. Presented at American Society of Nephrology Kidney Week; November 2-5, 2023; Philadelphia, PA. #TH-PO645

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