Clinical and Histological Correlations in C3 Glomerulopathy

Jillian Hall[1], Lauren Fergus[1], Monica Hall[1,2], Patrick D. Walker[3], Richard J. H. Smith[1,2], Carla M. Nester[1,2]
[1]Molecular Otolaryngology and Renal Research Laboratories, [2]University of Iowa Hospitals and Clinics, [3]Arkana Laboratories

Background

- C3 Glomerulopathy (C3G), defined by persistent dysregulation of the alternative pathway of complement and characterized by dominant C3 deposition on kidney biopsy is a rare kidney disease. >50% of patients progress to ESKD within 10 years.
- We sought to examine the correlation between histologic characteristics of the baseline kidney biopsy and various clinical parameters in a cohort of patients with C3G.

Methods

- 96 C3G patients from the University of Iowa's C3G Natural History Study were included in the cohort.
- Criteria for cohort inclusion: a baseline native kidney biopsy diagnosis of C3G, availability of serum C3 levels and UP/C at presentation and at follow-up, and a GFR >30 mL/min/1.73m^2 at initial evaluation.
- Chronicity on biopsy was defined as either None to Mild or Moderate to Severe. Acuity markers were coded as focal/segmental or diffuse/global.
- Pearson correlation coefficients with two-tailed p values (95% confidence) were used to examine disease-related parameters. "Yes/No" parameters were coded 1/0 for correlation calculations. One-way ANOVA analysis was used for figures 3-7.

Results

Chronicity:

- 56% of the cohort presented with glomerulosclerosis on baseline biopsy, 7% presented with 50% sclerosis or greater. Greater severity of glomerulosclerosis at onset was associated with a higher baseline C3 (R = 0.443, p = 3.508e-005). Increased severity of glomerulosclerosis (R = -0.617, p = 4.395e-011), interstitial fibrosis (R = -0.461, p = 3.678e-006), and tubular atrophy (R = -0.431, p = 1.82e-005) were associated a lower GFR at onset.
- 50% of patients presented some degree of interstitial fibrosis, 25% of which was moderate or greater. 49% of the cohort presented tubular atrophy, 21% of which was moderate or greater. Of the 12 patients with moderate or greater tubular atrophy, 9 patients also had moderate or greater interstitial fibrosis. The lowest observed onset GFR in patients without interstitial fibrosis or tubular atrophy was 94 mL/min. The significance of the comparison between levels of severity on the histological markers shown in figures 6 and 7 indicates that greater severity of interstitial fibrosis and tubular atrophy on baseline biopsy is correlated with lower GFR at onset.

Acuity:

- 75% of the patients in the cohort presented with diffuse or global mesangial hypercellularity.
- Presence of mesangial hypercellularity at onset was associated with lower baseline C3 (R^2 = 0.09597, p = 0.0186) and a progressive increase in UP/C (R = 0.257, p = 0.019).
- 48% of the cohort presented with diffuse or global endocapillary proliferation. A diffuse/global presentation was significantly correlated with lower onset C3 (R^2 = 0.1735, p = 0.0006).
- 25% of the cohort presented diffuse or greater leukocyte infiltration. Increasing severity of leukocyte infiltration was associated with lower onset C3 (R^2 = 0.1707, p = 0.0007).

Treatment:

- 67.7% of patients in this cohort received immunosuppressive treatment during their disease course. No significant correlation was noted with change in GFR (R = 0.071, p = 0.516), C3 (R = 0.163, p = 1.45), or in UP/C (R = 0.151, p = 0.168).
- 89% of patients received ACEi/ARB medications during their disease course. Treatment with ACEi/ARB medications also showed no significant correlations with change in GFR (R = -0.186, p = 0.084), C3 (R = -0.162, p = 0.147), or UP/C (R = -0.075, p = 0.497).

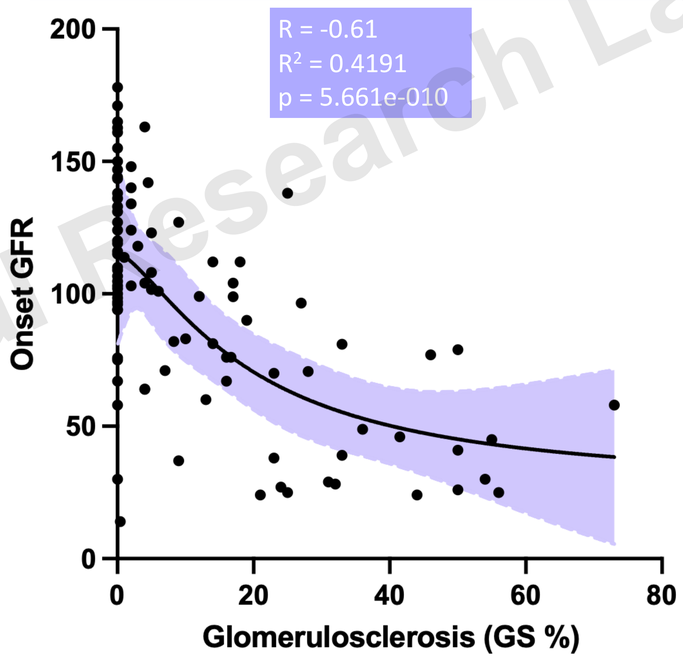
Conclusions

- Greater degrees of mesangial hypercellularity, endocapillary proliferation and leukocyte infiltration were associated with a lower presentation C3 – (suggesting an association with a greater degree of complement activation).
- For histologic markers of acuity, similar findings were also correlated with a rising UP/C over time.
- As others have seen, there was no correlation with traditional immune suppression and change in UP/C or GFR over time.
- Similarly – we found a statistically significant correlation with markers of chronicity and risk for GFR loss.
- Limitations of this study include, the baseline heterogeneity of the population and the availability of complete histologic parameters on a larger data set.

References

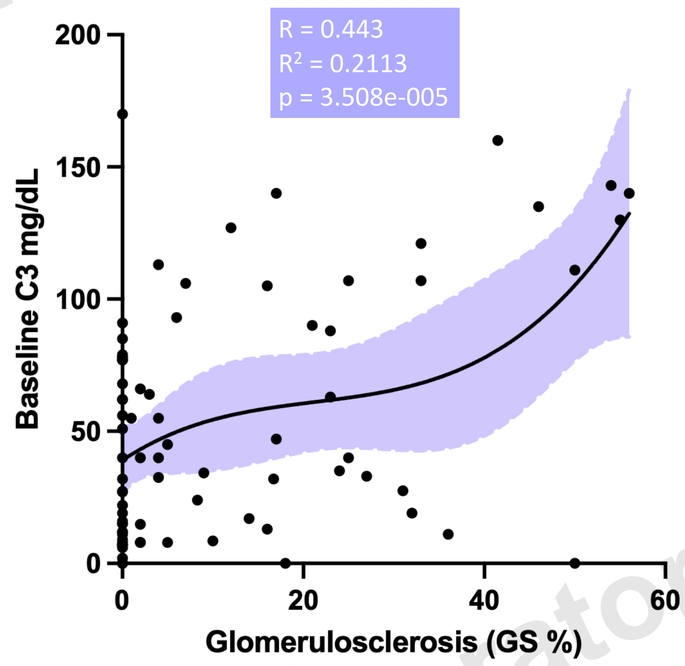
1. Kidney Int. 2018 Apr;93(4):977-985
2. Clin J Am Soc Nephrol. 2022 Jul;17(7):994-1007

Figure 1: Onset GFR vs. Glomerulosclerosis (GS %)



Line is sigmoidal fit, purple shaded area represents 95% confidence.

Figure 2: Onset C3 vs. Glomerulosclerosis (GS %)

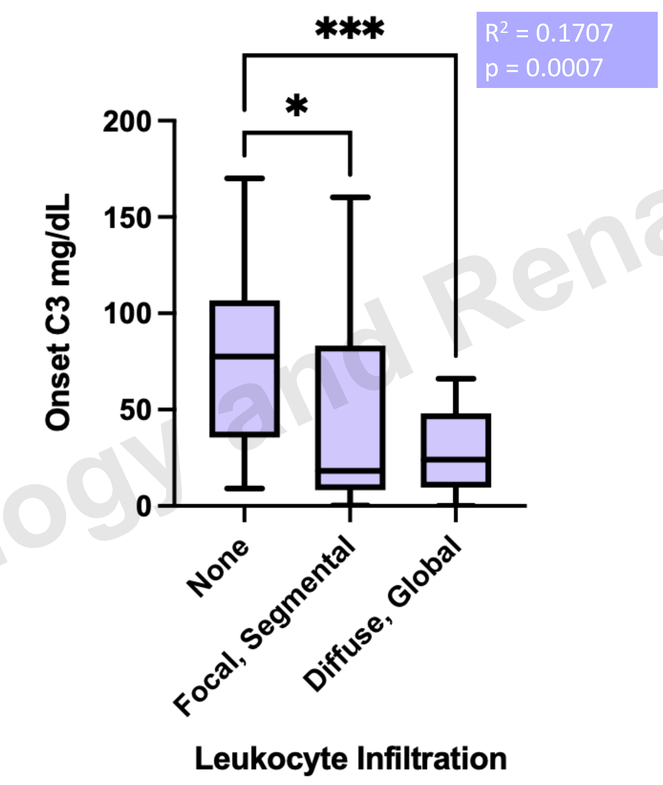


Line is cubic fit, purple shaded area represents 95% confidence.

Figure 3: Onset C3 vs. Mesangial Hypercellularity

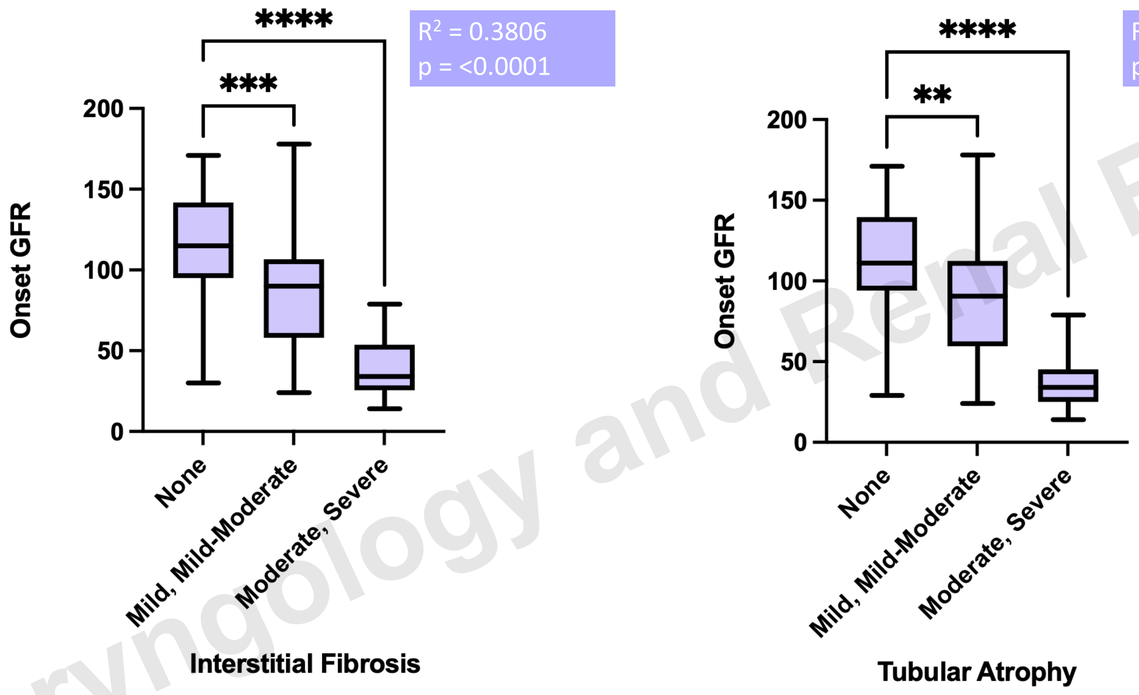
Figure 4: Onset C3 vs. Endocapillary Proliferation

Figure 5: Onset C3 vs. Leukocyte Infiltration



- Figures 3-5 represent statistically significant results using a 95% confidence interval. A score of 1+ or 2+ for a histological marker on the pathology worksheet represents focal or segmental presence of the histological marker, where 3+ and 4+ represent diffuse and global presence of the marker. One-way ANOVA was used to examine comparison between the markers to determine whether increased severity was significant, rather than the presence or absence of the marker.
- Figure 6 represents statistically significant results using a 95% confidence interval. A score of 0.5, 1.0, or 1.5 on the pathology worksheet represents mild to mild-moderate presence of the histological marker. A score of 2.0 to 3.0 represents moderate to severe presence of the marker. One-way ANOVA was used to examine comparison between the markers to determine whether increased severity was significant, rather than the presence or absence of the marker.

Figure 6: Onset GFR vs. Interstitial Fibrosis and Tubular Atrophy



Molecular Otolaryngology & Renal Research Laboratories

University of Iowa Stead Family Children's Hospital

Supported in part by the Bruder family and NIDDK R01 110023.
We thank those patients with C3G who have made this research possible.