Longitudinal Complement Biomarker Trend in C3 Glomerulopathy

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Background

C3 Glomerulopathy (C3G) is an aggressive form of complement-mediated kidney disease that primarily affects children and young adults.[1] No disease directed therapeutics are available. Greater than 50% of those affected progress to end stage renal disease within 10 years of diagnosis.[2] Little is known of the natural history of disease and disease related biomarkers. Our goal was to describe the trend in C3 (a protein with a central role in the complement system) and the trend in renal filtering function over the duration of disease. In addition, we sought to describe the relationship between these two disease related biomarkers.

Methods

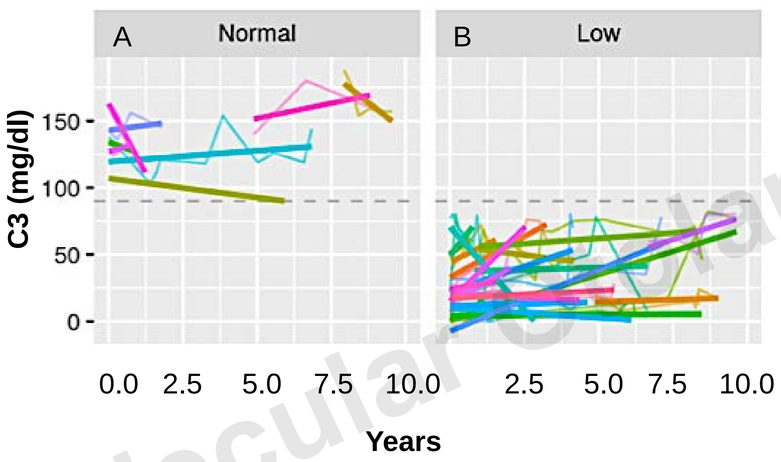
Study subjects included 50 C3G patients from the University of Iowa's C3G Natural History Study Cohort. All patients met the consensus definition for C3G[3]. Eligible subjects had more than one year of disease, at least three C3 levels, multiple estimates of renal function and a known complement genetic background and nephritic factor status. Trend tests were applied to each patient's C3 and estimated renal function (eGFR).

Results

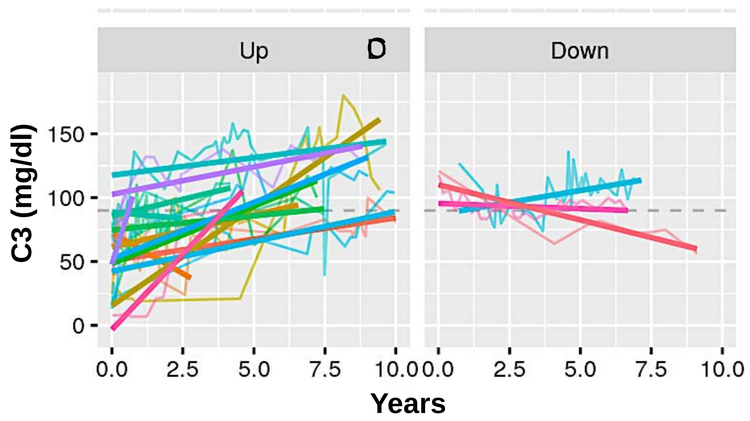
Median follow-up was 7.18 years (range 1-32 years). 20 (40%) patients had evidence for a nephritic factor. Nine (36%) had a pathogenic gene mutation.

C3 Trend:

1. 8 of 50 (16%) patients had a normal C3 at diagnosis and continued to have a normal C3 throughout follow-up. (A)
2. 22 of 50 (34%) patients maintained a low C3 across all time points. (B)



3. 21 of 50 patients (44%) had a low C3 at diagnosis however recovered into the normal range at some point during follow-up. (C)



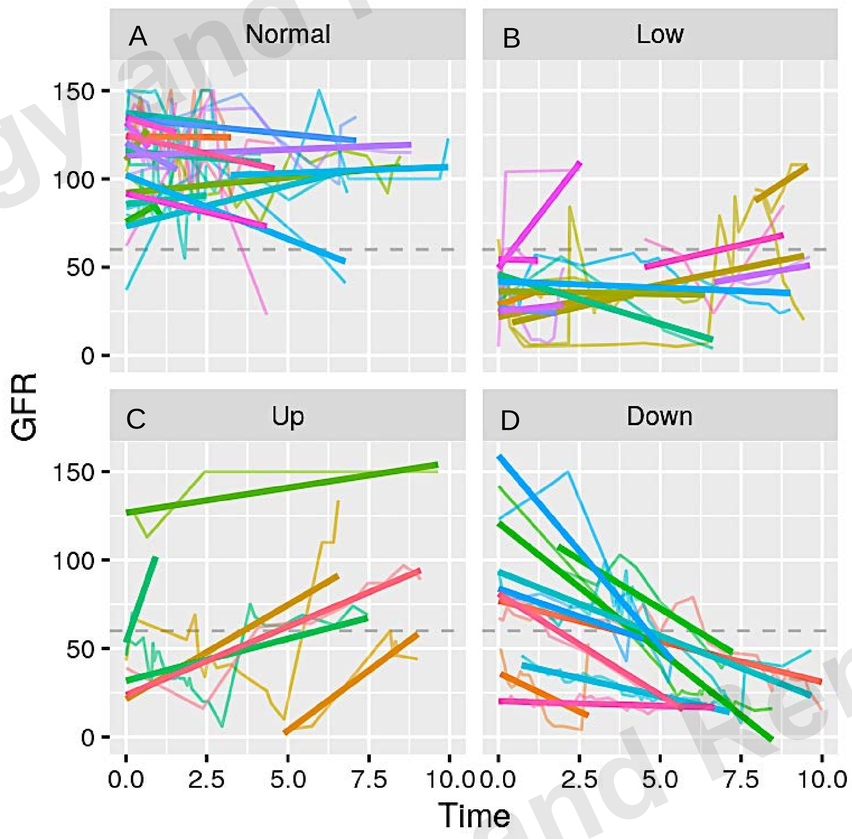
Results

C3 Trend:

4. 70% of those that normalized did so within the first two years of diagnosis.
5. 10% of those that normalized remained in the normal range throughout all time points of follow-up.
6. 13 of 50 (26%) had a significant/persistent trend upward over the course of follow-up.

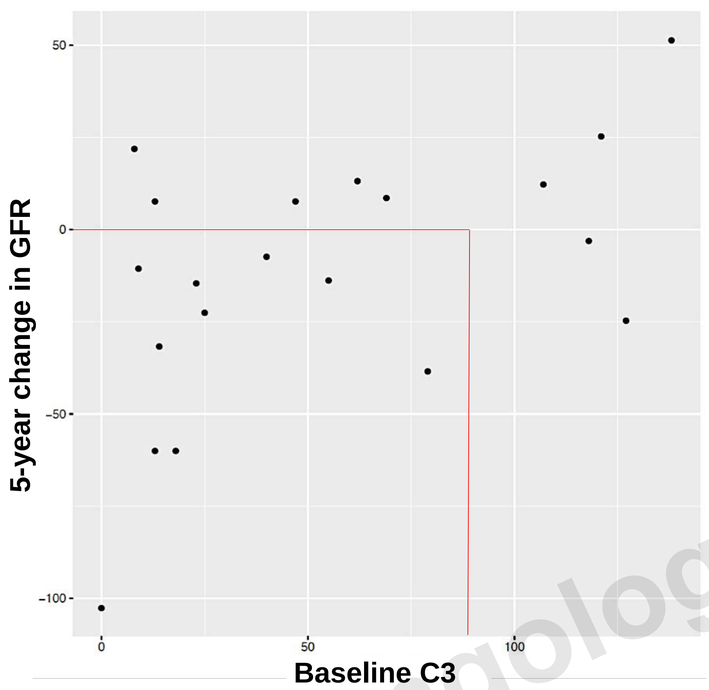
Estimated GFR (eGFR) Trend

1. 18 of 50 (36%) patients presented with and retained a normal GFR across follow-up visits. (A)
2. 11 of 50 (22%) presented with a low eGFR. (B)
3. 7 of 50 (14%) patients experience an improvement in their eGFR over time. (C)
4. 14 of 50 (30%) patients had a significant decline of their eGFR during the study period. (D)



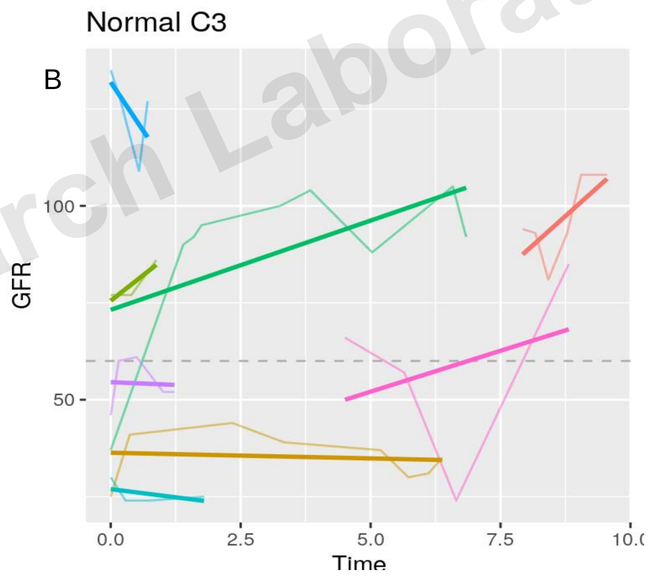
Relationship between C3 and GFR

1. Among the patients whose GFR went down, C3 went up in 4 and down in 1 (9 others with no clear trend).
2. Among the patients whose C3 went up, GFR went down in 4 patients and up for 2 patients (7 others with no clear trend).



Results

3. On average, patients with a lower C3 at baseline experienced a greater decline in GFR over the first five years of their disease (p=0.02).(A-C)



Conclusions

- 1/6th of C3G patients presented with a normal C3.
- Normalization of the C3 within the first 2 years of diagnosis was common.
- In this cohort, a lower C3 predicted a greater risk for declining eGFR.

Future Directions

The study team is in the process of expanding the cohort size, looking specifically at environmental modifiers (transplant, dialysis, terminal complement blockade exposure) and correlation with a larger panel of clinical and complement biomarkers.

References

1. Pediatr Nephrol. 2012 May;27(5):773-81
2. Nat Rev Nephrol. 2019 Mar;15(3):129-143
3. Kidney Int. 2013 Dec;84(6):1079-89

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