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Identifying C3G: Key Diagnostic Considerations and Challenges

Dr. Colbert:
Welcome to *On the Frontlines of C3G* on ReachMD. I'm Dr. Gates Colbert, and joining me to discuss diagnostic challenges in complement 3 glomerulopathy is Dr. Anuja Java, who's an Associate Professor of Medicine in the Division of Nephrology at Washington University School of Medicine and the Director of the Kidney Transplant Clinic at John Cochran Veterans Hospital in Missouri.

Dr. Java, welcome to the program.

Dr. Java:
Thanks for having me, Dr. Colbert. It's a pleasure to be here.

Dr. Colbert:
To start us off, Dr. Java, could you provide us with some background on C3G?

Dr. Java:
Sure. So C3G, or C3 glomerulopathy, is a glomerulonephritis, which is considered a rare disease and thought to be due to a dysregulated complement system—particularly the alternative pathway—and it is characterized by the predominant deposition of C3 in the glomerulus, and by predominant, typically on a biopsy, we think of it as two orders of magnitude higher than any other immunoglobulin as present. And because it's a rare disease, typically we think of an incidence about 1 to 3 per million or a prevalence of 5 per million. But some of these numbers are confounded by regional differences in practices of biopsy and referrals. But overall, it's a GN like many other GNs.

Dr. Colbert:

Now, why is C3G so difficult to diagnose, and how might diagnostic delays adversely impact patients?

Dr. Java:
There are several reasons why there are delays in diagnosis particularly with C3G even though we think this is a glomerulonephritis. So first of all, there is no serum test or biomarker that helps us diagnose what this disease is, so there is no specific complement testing that you can do and it will tell you that this is C3G.

The second issue is because it is a glomerulonephritis, its clinical features can manifest like any other GN. And more importantly, C3G is a very heterogeneous disease, so patients can actually have features ranging from being asymptomatic for a long time with C3G just brewing in the kidney and nothing shows up clinically in these patients; they can just present with some hematuria; there may be patients that have hematuria and proteinuria; and then you have this subset of patients that will present with this full-fledged GN picture.

In addition to this heterogeneity, you really need a biopsy to get that this is C3. And because biopsy practices can vary sometimes when physicians see a hematuria or proteinuria, they might just think that this is IgA nephropathy, or they might presume this is something else more common, and a biopsy may not happen in time. So there are several reasons why there's a lack of timely diagnosis. And I also think that, traditionally, when physicians have this mindset that this is a rare disease, they're not thinking of it and it's not in their differential. So many times, that leads to delays in diagnosis as well.

Dr. Colbert:
For those just tuning in, you're listening to *On the Frontlines of C3G* on ReachMD. I'm Dr. Gates Colbert, and I'm speaking with Dr. Anuja Java about diagnostic challenges in complement 3 glomerulopathy.

So, Dr. Java, when it comes to kidney biopsy and its role in diagnosis, why is there a gap between clinician and patient perception?

Dr. Java:
We've just talked about how kidney biopsy is absolutely essential to make a diagnosis for C3G, and not only to make a diagnosis, but also to ascertain how active the disease is and if there are chronic changes. And from a physician perspective, we know it's critical, but it's an invasive procedure. And because as physicians we have so much experience with it and we do it for so many of our GN patients, we know that overall, in general, it's thought to be safe; it has a low incidence of complications. Bleeding, of course, can happen. There can be some pain. But for the most part, those are not common. And many times, these patients don't even need to stay in the hospital beyond a few hours.

But from a patient perspective, for whom this is the only time they've seen this disease and they haven't gone through multiple biopsies, it can be a little daunting. It is, of course, invasive. And particularly if the procedure is not explained to the patient—even if it is explained, if they go through some kind of pain or there is any complication, they could have an adverse experience associated with it.

More importantly, with C3G, even for trials and going forward, because these patients present histologically much earlier than they present clinically, sometimes we think that they need multiple biopsies and protocol biopsies. And all of that can really play heavily for our patients. In fact, we have written about this. I actually published a perspectives paper in *Kidney Medicine* where I have put together a clinician perspective, and my co-author is actually a patient with C3G, and we've put together our perspectives on C3G, and there's a whole topic on biopsies. And Lindsay, my co-author, outlines how her biopsy experience was not very smooth. And I think if that's the case with some other patients, it might change how they view biopsy and how as physicians we view this particular procedure.

Dr. Colbert:
And finally, Dr. Java, do you have any insights on addressing diagnostic challenges in C3G that you'd like to share?

Dr. Java:
As a field, we have come a long way, number one, in recognizing the role of complement in multiple diseases—not only C3G. In fact, we called it MPG a few years ago, and that was primarily based on what was seen on the biopsy—just the pattern—and as our understanding of complement-mediated diseases and the role of complement, particularly in these diseases, has improved, we've recognized this as a separate entity. So I think we've come a long way in what we understand, the pathophysiology, and the treatments that are available to us, but yes, there are still quite a few things that are lacking. Like I mentioned, other than doing a biopsy, we don't have a ready-set biomarker that we need, and that is one challenge. There are labs that are working on it, and so I'm very optimistic that in the years to come, we're going to make more progress, and we'll probably have a set of biomarkers that will help us identify these patients earlier.

In addition, this is a disease of a dysregulated complement system of the alternative pathway, and that dysregulation occurs because of genetic mutations and acquired factors. And so even though we don't need that in diagnosing this disease, we do need some of that testing to establish the etiology, the prognosis, and how long you're going to treat these patients. But right now, not all labs offer these testings. Genetic testing has improved, but it's available in few labs.

And more importantly, acquired factors are such an important cause of C3GN—those acquired factors and nephritic factors—and there's a lot of heterogeneity in what these nephritic factors mean, even if you identify them. There are very few labs that offer it, so that adds to that diagnostic challenge or establishing what you want in the pathophysiology for your patient. And better characterization of these biomarkers and these nephritic factors are needed for the future. Of course, we've talked about biopsy, but for better or for worse, until we have these biomarkers, we're going to need to be doing early biopsies and more protocol biopsies to better diagnose and diagnose timely.

Dr. Colbert:
Yes, I fully agree. And as a nephrologist myself, I can attest that the clinical experience of most nephrologists in the United States is very limited with C3G. Because it is a rare disease, it's hard to see good cases and see them for the long-term follow-up. So that is a challenge that we have and an education point that we need to just reignite as we now have better treatments for C3G and C3GN.

I want to thank my guest, Dr. Anuja Java, for joining me to discuss how we can address challenges in diagnosing patients with C3G. Dr. Java, it was great having you on the program.

Dr. Java:
Thanks for having me, Dr. Colbert.

Dr. Colbert:
For ReachMD, I'm Dr. Gates Colbert. To access this and other episodes in our series, visit *On the Frontlines of C3G* on ReachMD.com,

where you can Be Part of the Knowledge. Thanks for listening.