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Improving the Early Detection & Diagnosis of C3G

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is sponsored by Novartis Pharmaceuticals Corporation. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss how we can improve the early detection and diagnosis of complement 3 glomerulopathy, or C3G for short, is Dr. Kenar Jhaveri. Dr. Jhaveri is the Associate Chief in the Division of Kidney Diseases and Hypertension at Northwell Health and Zucker School of Medicine at Hofstra Northwell. Dr. Jhaveri, thanks for being here today.

Dr. Jhaveri:
Well, thank you, Charles.

Dr. Turck:
So let's start with some background, Dr. Jhaveri. Would you define C3G for us and tell us about the role of the alternative complement pathway?

Dr. Jhaveri:
Thanks, Charles. C3GN is sort of a relatively newer diagnosis that people have used, I would say, since 2010 almost. Before that, this disease used to be called the old MPGN, or membranoproliferative glomerulonephritis type 2 or 3. So if you look at the old textbooks, that's what this is. So it turns out that in 2007, people realize that the old postinfectious glomerulonephritis, or some sort of complement-mediated process, is really a C3 glomerulopathy, or an overactivation of the alternative complement pathway. So that's, in a gist, the immunological reason how you get C3GN. So normally, our alternative pathway is activated at another level, but in C3GN, it becomes overactivated for certain reasons. It could be an infection, it could be autoimmunity, or genetics might play a role in addition to all the above. And that's what C3GN is. And that's from the alternative complement pathway. So you could have a lot of reasons for that to happen. You can have just too much of overactivation, or you could have an inhibitor of the sort of the brakes that happen in the immune system. If you have an inhibitor to the brakes, like factor H, for example, or factor I, then your immune system is overactive also. So in that case, that's what happens in these situations.

Dr. Turck:
Well with that in mind, what are some of the most common signs and symptoms of C3GN we should be on the lookout for?

Dr. Jhaveri:
I mean, it's unfortunately a silent disease unless someone checks a urinalysis, and you notice some hematuria or proteinuria. You're not going to have symptoms of renal failure until much later. In some cases, you do get an upper respiratory infection and following that, the renal disease happens. So that would be a clue. Strep is a common one, but usually, it's urinary findings and elevation in creatinine or renal failure, and hypertension. Those are usually the first signs but often missed because a lot of these patients are young and don't see a doctor. And even if you do have hypertension, a lot of times that's not triggering a checking your urine or checking for proteinuria from an internist. So I think that's why a lot of these diseases get picked up much later in the disease process than earlier.

Dr. Turck:
And once we have suspicion of disease, what do we need to do to confirm a diagnosis?

Dr. Jhaveri:

I mean, while we can do all these lab tests of complement testing and so forth, the gold standard really is a kidney biopsy. If there's no major contraindication, a quick kidney biopsy is so key because that actually clinches the diagnosis. In addition, you can send complement studies, but some of them do take a while, and in some of the labs in the rest of the world or even here in the U.S., there are a few that do detailed complement testing to confirm the diagnosis.

Dr. Turck:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Kenar Jhaveri about strategies for improving the early detection and diagnosis of complement 3 glomerulopathy, or C3GN.

So Dr. Jhaveri, now that we have a better understanding of how to diagnose C3GN, let's focus on how we can optimize our approach. First, are there any common diagnostic barriers we should be aware of?

Dr. Jhaveri:
Thanks. That's a very important question, Charles. I think the biggest diagnostic barrier is getting the complement testing done. So for example, we get a lot of these patients who we do a kidney biopsy show C3GN, and the C3 could be low in, say, 60 percent of the patients, but 40 percent of C3 is not low. And then you still want to know if there's activation of that terminal pathway in the complement cascade, the MAC complex. And that is a special test that's a send-out. A lot of these send-out tests happen in a specialized lab; they do a full complement panel, which does not include just C3 and C4, but the MAC complex, factor H, factor I, and so forth. So you want to know what those levels are. In addition, you want to know with genetic testing if they have a mutation in one of those levels, and that is very important. You know, sending C3 nephritic factor, that's not available at other centers either. So those are the things that are very challenging, and only certain labs can do and can be time restraining. And that's the biggest challenge in making the diagnosis of C3GN.

Dr. Turck:
Now with that being said, what can we do to overcome those barriers and reduce diagnostic delays?

Dr. Jhaveri:
I think one of the biggest barriers to that is to really try to have, say, perhaps local labs able to do some of these testing and more availability of these labs around the country to do the specialized testing. I think those are the two most important ways to kind of overcome those barriers.

But in addition, I think the biggest thing is understanding the disease upfront. I think the diagnosis happens so late because the referral to nephrology perhaps is too late because nobody checked a urinalysis with someone with hypertension who's young. And that then does not lead to an early kidney biopsy, which then leads to a late kidney biopsy, a late referral, and not much you can do despite these testings and treatment options.

Dr. Turck:
Now before we close, Dr. Jhaveri, what kind of impact could a timely diagnosis have on the overall management of patients with C3GN?

Dr. Jhaveri:
Again, the management is very challenging. So let's talk a little bit about management, and we'll call in terms of the impact. The management usually is steroids and mycophenolate. And that's the standard of care usually for these patients if they have moderate amount of disease. If mild, it's just supportive therapy with ACEs, ARBs, and so forth. But if they don't respond to the therapy with mycophenolate and steroids, usually it's reserved to give anti-complement therapy such as eculizumab or others that might be in the pipeline.

And in my opinion, I think the best thing for these patients is really to get them into a clinical trial because that is where you can learn a lot about the disease, and at the same time, get them potentially the best treatment that directly attacks the crux of the problem. It's a challenge to get them treated because the disease is picked up very late. And hence, the damage on the kidney biopsy, the fibrosis, is significant. And that leads to an early end-stage kidney disease diagnosis, leading to dialysis, and eventually transplant. And if not treated well, there's a good chance of recurrence of the disease against post-catheter kidney transplant as well.

Dr. Turck:
Do you have any final thoughts you'd like to share with our audience about C3GN?

Dr. Jhaveri:
I think it's important that people realize it's still a very rare disease. And I think this is one of those diseases where you need an expert glomerular disease center to take care of these patients, along with maybe a general nephrologist. So this is the one disease where I think people should ask for help if they're not sure how to treat it because you might treat one in five years perhaps, and that's why it's important for people to know their limitations when they treat rare diseases.

Dr. Turck:
Well given the importance of a timely diagnosis, I want to thank my guest, Dr. Kenar Jhaveri, for providing insights on how we can reduce diagnostic delays and detect C3GN early. Dr. Jhaveri, it was great having you on the program.

Dr. Jhaveri:
Well, thank you, Charles. Thank you.

Announcer:
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