Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/clinicians-roundtable/examining-the-mechanisms-diagnosis-of-c3g/14908/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Examining the Mechanisms & 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:
Welcome to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and joining me to examine the role of the alternative complement pathway in complement 3 glomerulopathy, or C3GN for short, is Dr. Sanjeev Sethi. Dr. Sethi is a Professor in the Department of Laboratory Medicine and Pathology who specializes in the diagnosis of kidney diseases at Mayo Clinic in Rochester, Minnesota. Dr. Sethi, thanks for being here today.

Dr. Sethi:
Thank you Charles.

Dr. Turck:
So let's just dive right in, Dr. Sethi. What can you tell us about the pathophysiology of C3GN and the history of our understanding of it?

Dr. Sethi:
So C3 glomerulopathy is a disease entity that is characterized by overactivation of the alternative pathway of complement. Once you have overactivity of the complement pathway, these complement fragments are then deposited in the glomeruli. Once you have excess deposition of complement fragments, it drives inflammation and that causes glomerular nephritis. The term "C3 glomerular nephritis" is coined because C3 is the dominant complement protein that is detected in the glomeruli, and that's where the term "C3 glomerulopathy" comes from. C3 glomerulopathy, although it's been described recently, it doesn't mean it's a new disease entity. The disease entity just went by a different name in the past. It was called membranoproliferative glomerulonephritis, in short MPGN. So the term MPGN was used for a long time and, in fact, was further classified into MPGN 1, MPGN 2, and MPGN 3 based on the path and on electron microscopy. But clearly, studies have shown that what we used to call MPGN 1, some of MPGN 3, and a lot of MPGN 2 actually are what's now characterized as C3 glomerulopathy, resulting from overactivity of the complement pathway, and particularly the alternative pathway of complement.

Dr. Turck:
Alright, so looking a little bit more at the alternative complement pathway, what more could you tell us about its dysregulation and how that might lead to disease progression and kidney damage?

Dr. Sethi:
So the alternate pathway is regulated very seriously. I mean, there are multiple checks and balances in the alternative pathway of complement, and because of these multiple checkpoints, the complement pathway stays in check. So for example, if a person gets infection, the alternative pathway is critical for managing the infection, but once the infection goes away, the alternative pathway goes back into the basic baseline. And so on. But once you have any abnormality in the alternative pathway – could be an autoantibody to the checkpoints like I just told you, or there could be a mutation in some of these proteins that regulate the alternative pathway – either one of those can result in overactivity of the alternative pathway. So in other words, once the alternative pathway kicks up, it does not go back to its normal state, and it stays in overdrive. This overdrive of the alternative pathway leads to deposition of complement fragments in the glomerulus, which in turn leads to inflammation.

Dr. Turck:

© 2023 ReachMD

Now how might our knowledge of the alternative complement pathway help direct us to therapeutic targets?

Dr. Sethi:
You need to know a detailed sort of map of the alternative pathway, number 1. Number 2 – you need to know where the abnormality is – is it upstream? Is it in Factor H? Or is it an autoantibody to the C3 convertase, which is also called nephritic factor? Or is it downstream? So it's really important to know where the abnormality lies, and once you know where the abnormality lies, probably down the road – right now, we don't have drugs targeting specific proteins – but down the road, you may have targeted treatment available for C3G.

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. Sanjeev Sethi about the mechanisms of disease in complement 3 glomerulopathy, or C3GN.

So, Dr. Sethi, now that we have a better understanding of the alternative complement pathway's role in C3GN, let's focus on how we might detect this rare kidney disease. What does the diagnostic process look like?

Dr. Sethi:
So when a patient comes to the nephrologist, and the nephrologist sees that the patient has low C3 titers, has hematuria and proteinuria, and other causes of low complement – for example, monoclonal immunoglobulins, autoimmune diseases, and infections – are ruled out, then you start thinking that this could be C3 glomerular nephritis. A kidney biopsy is then performed.

Dr. Turck:
And as a pathologist, how do you confirm a diagnosis of C3GN?

Dr. Sethi:
The kidney biopsy is characteristic. The kidney biopsy on light microscopy shows a proliferative glomerular nephritis. In other words, the glomeruli show lots of cells. There really are patterns of injury on the glomerulus, and one of the most common patterns is called MPGN, or membranoproliferative glomerulonephritis, and most cases of C3 glomerular nephritis present with this MPGN pattern. MPGN pattern is what tells you that the lesion has been going on for a few weeks, if not months, and what you see in an MPGN pattern is a glomerulus that looks very hypercellular. There are lots of cells in the mycangium, there are lots of cells in the capillary loops, the capillary walls are thickened, and the thickening results from accumulation of this complement material resulting from overactivity of the alternative pathway. There are double controls that form along the capillary walls; in other words, the complement is now sort of embedded among various layers of the basement membranes. So all of these features characterize what's called MPGN. It's called a membranoproliferative glomerulonephritis pattern of injury.

So based on this particular pattern on light microscopy, the next thing we do is immunofluorescence microscopy. The IF shows characteristic C3. It's bright C3 – as bright as you can imagine – which clearly reflects a lot of complement that is deposited in the glomeruli. One of the things that you can tell this is C3G and not something else is the fact that the immunoglobulins are very little or absent. So on immunofluorescence, as a pathologist, I stain for IgA, IgG, IgM, C1q, C3, and kappa and lambda light chains. Everything is negative except for C3, so IgA, IgG, and IgM is negative or there might be a small amount sort of entrapped there. C1q, which is a complement protein coming from the classical pathway, is also absent, so all that we're left for is a large amount of C3. So when I see an MPGN pattern on light microscopy, bright C3 on immunofluorescence, negative immunoglobulin, IGa, IgG, Igm, kappa, and lambda – including C1q – then I'm pretty sure that this is C3 glomerular nephropathy. To confirm that, we do electron microscopy. Now in electron microscopy when you see a lot of capillary wall deposits along with some mesangial deposits, you know this is C3GN.

Dr. Turck:
Now we have certainly covered a lot of ground today, so before we close, Dr. Sethi, are there any key takeaways you'd like to share with our audience?

Dr. Sethi:
I think that the most important thing is that we've moved on from the MPGN story, which was not driven by etiology, to now identifying C3 glomerulopathy with a clearly defined etiology that is overactivity of the alternative pathway of complement. We have come a long way in now identifying the various places where the overactivity results from – mutations and autoantibodies – to the various regulating proteins. I think the key is to identify the etiology that's driving the alternative pathway of complement, and then in the future, being able to target this very specific abnormality.

Dr. Turck:
And with that, I want to thank my guest, Dr. Sanjeev Sethi, for joining me to discuss the role of the alternative complement pathway in C3GN. Dr. Sethi, it was great having you on the program.

© 2023 ReachMD

Dr. Sethi:
Thanks, Dr. Turck.

Announcer:
This episode of *Clinician's Roundtable* was sponsored by Novartis Pharmaceuticals Corporation. To access this and other episodes in this series, visit ReachMD.com/Clinician's Roundtable, where you can Be Part of the Knowledge. Thanks for listening!

© 2023 ReachMD