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IgAN Insights: The Potential Role of the Complement System in Disease Progression

Announcer:
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Dr Francis:
Welcome, everyone, to a podcast on IgA nephropathy and its connection to the complement system. My name is Dr Jean Francis. I'm an Associate Professor of Medicine at the Chobanian & Avedisian School of Medicine at Boston University. I'm the Medical Director of the Kidney Transplant Program at Boston University Medical Center. I am also the Co-Director of the Thrombotic Microangiopathy Center of Excellence at Boston University Medical Center, managing so many complement-mediated diseases. Over the past 15 years of my clinical practice, I have also managed many patients with IgA nephropathy pre and post kidney transplant. In this podcast I will talk about IgA nephropathy and answer some frequently asked questions about the role of the complement system and its pathophysiology.

So, let's dive in. The first question that I hear a lot from my colleagues is how heterogeneous is IgA nephropathy in terms of its clinical features?

IgA nephropathy is a highly heterogeneous disease, with a wide array of clinical presentation that varies from patient to patient. There is significant heterogeneity across different racial and ethnic population in the epidemiology, in the presentation, the rate of progression, and the long-term outcomes of IgA nephropathy. The heterogeneity of clinical and pathological features as well as disease progression journey of IgA nephropathy involves a tailored approach to care. Some patients are asymptomatic with microscopic hematuria and/or proteinuria. Others are symptomatic and may present with gross hematuria, foamy urine, loin pain syndrome, discomfort. In my practice, most commonly, 80 to 90% of my patients present with hematuria and proteinuria with or without some decline in eGFR and kidney function. Up to 40% of patients with IgA nephropathy develop worsening kidney function and progress to kidney failure within 10 to 20 years of diagnosis. Patients may also have varying complement serum level. By that, I mean C3 and C4 levels, but hypocomplementemia is typically rare in IgA nephropathy. Let's talk about the complement system. The complement system is an innate component of the body's immune system and it is comprised of three pathways: alternative pathway, lectin pathway, and the classical pathway. Overactivation of the alternative pathway or less often the lectin pathway contributes to inflammation and host-cell injury. Discussion about the complement system and its pathways often leads to another important question that I hear.

How does complement activation fit into the four-hit model of IgA nephropathy?

First, let's review the four-hit model. In IgA nephropathy, the fourth hit of the multi-hit model activates the complement system. Hit one, there is an increase in galactose-deficient IgA1 antibodies production. Hit two, there is an induction of an autoantibody that is able to recognize this galactose-deficient IgA1 as an autoantigen. Hit three, this autoantibody binds to the galactose-deficient IgA antibodies and they form immune complexes that are circulating in the blood and the plasma. In hit four, the immune complexes will deposit in the kidney, typically in the mesangium, and they can activate the complement system, contributing to kidney damage. In my experience, the specific contribution of each hit can vary among individuals, and the relative importance of these hits may also depend on the genetic and the environmental factors. In some cases, complement dysregulation is a key driver of glomerular inflammation in IgA nephropathy.

My colleagues frequently discuss how does the complement system drive the progression of IgA nephropathy?

Activation of the alternative pathways and, less often, lectin pathway can cause mesangial cells to proliferate and produce cytokines and extracellular matrix proteins. This can result in progressive glomerular injury that manifests as hematuria and proteinuria. Unlike the classical or lectin pathway, the alternative pathway has feedback loop mechanisms that amplifies the cleavage and the production of active C3. This leads to increased complement deposition, kidney inflammation, and kidney damage.

Continuing with this topic, another question I get asked is, what evidence exists to support the activation of the complement system in IgA nephropathy?

Biopsy and serological studies provide supporting evidence for the role of the complement system in IgA nephropathy. In biopsy studies, C3 deposition is present in up to 90% of the patients with IgA nephropathy. The level of C3 accumulation in the glomeruli can vary between patients and may be an indicator of prognosis. Co-deposition of IgA, C3, and properdin highlights the activation of the alternative pathway in IgA nephropathy patients. Plasma levels of factor Ba are also indicators of alternative pathway activation and have been shown to be elevated in patients with IgA nephropathy. Positive immunofluorescence on kidney biopsy staining for both glomerular factor Bb and C3 demonstrates activation of the alternative pathway.

Another common question is, what does complement system dysregulation mean for patients with IgA nephropathy?

In my experience, assessing a combination of predictors, including complement system involvement, may be helpful to identify individuals who are most likely to progress to end-stage renal disease. Complement activation contributes to glomerular inflammation, and inflammation can lead to more extensive kidney damage, higher risk for kidney function decline, and exacerbation of proteinuria.

Along with the impact on patients, my colleagues sometimes ask, what does thinking of IgA nephropathy as a complement-mediated disease mean for providers?

In my opinion, the recent focus on data surrounding the complement system role raises important questions as to whether nephrologists should reassess their understanding of IgA nephropathy. In my practice, activation of the complement system is seen in multiple glomerulonephritis, which indicates activation of this pathway has broad clinical implications and significance for patient's outcomes. I believe nephrologists should continue to stay up to date on how IgA nephropathy pathophysiology is understood and is evolving within the nephrology field.

Thank you so much for listening. I hope that this podcast has reinforced the role of the complement in IgA nephropathy pathophysiology and has helped answer some of the common questions from nephrologists.