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Time needed to complete: 30m

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The 4-Hit Hypothesis: Foundations of IgAN Pathogenesis

Announcer:
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Dr. Lafayette:
Hi, this is Richard Lafayette and I'm presenting this CE on ReachMD. Today we'll introduce you to IgA nephropathy and review the 4-hit hypothesis of the pathogenesis of IgA nephropathy.

Again, IgA nephropathy is a disease of glomerular inflammation that can lead to injury and eventually to chronic kidney disease and the need for dialysis. It can only be defined by a kidney biopsy showing mesangial proliferation and the deposition of IgA in the glomerular mesangium by immunofluorescence.

As we know, this is the most common primary glomerular disease in the world, but it's still a rare disease. Such as in the United States, this occurs in about 4- to 8,000 new cases per year and probably involves somewhere between 120- and 200,000 individuals. We suspect it might be underdiagnosed because we don't have universal screening and because patients may present very late in their disease state and never be diagnosed, this is different than in other parts of the world where the prevalence is higher and where screening is higher as well.

So we see in Asian populations a much greater prevalence and incidence rate of IgA nephropathy. And the same is true in Northern Europe, in the United States. It's also more prevalent among patients of Asian background and among Hispanics. Again, these differences are likely related to genetics because, as we'll review in the 4-hit hypothesis, the disease is very prone to a genetic background, but there also may be other geographic differences in terms of environmental exposures, diet, and other issues.

Again, when we really come full circle and look at the pathogenesis of IgA nephropathy, it's nice to simplify it to the 4-hit hypothesis. And what that really suggests is that each of us has our genetic predispositions to diseases, including those who are predisposed to IgA nephropathy. And with the right genetic background, what can occur is that patients have a mucosal immune system that's predisposed to make more galactose-deficient IgA. And when there's stress in the mucosal surface, particularly after viral or other infections, there's a set point where there's increased production of galactose-deficient IgA, which ends up moving to the blood compartment leading to circulating levels of galactose-deficient IgA, which are persistently high. It's thought that these genetic differences also lead to a response to that galactose-deficient IgA that leads to elevated levels of an antibody against galactose-deficient IgA.

So in hit 1, you have elevated circulating levels of galactose-deficient IgA, and in hit 2, you have elevated levels of antibodies, be it IgG, IgA, or IGM, against that circulating galactose-deficient IgA. In turn, the increased antigen, the galactose-deficient IgA, and antibody, those antibodies against galactose-deficient IgA, form increased levels of circulating immune complex, which then bispecific receptors

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and nonspecific binding in the glomerular mesangium, which is trying to filter the blood, you end up with higher levels of immune complex in the glomerular mesangium so that IgA and those quad antibodies end up the glomerular mesangium where again, in the appropriate genetically predisposed individual that can lead to inflammation, leading to hematuria, leading to proteinuria, and that chronic inflammation eventually can lead to scar in the mesangium, in the glomerular podocytes and endothelium, leading to glomerular scarring and even downstream interstitial inflammation and interstitial scarring leading to progressive chronic kidney disease.

In thinking about that 4-hit hypothesis, it's very important to know that upstream, that it is B cells that can mature to antibody-producing cells, plasma blasts and plasma cells, which lead to the production of both the galactose-deficient IgA as well as autoantibodies to galactose-deficient IgA.

So with that 4-hit hypothesis, knowing the genetic predispositions, the contribution of B cells and plasma cells to the production of autoantibodies and the downstream inflammation being a result of cytokines and complement activation, the field of IgA nephropathy has become rich with hypotheses of mechanisms that can be blocked, and further episodes will focus on interventions to deal with this 4-hit hypothesis and the fact that it's driven by B-cell activation.

So hopefully this is a great start to the discussion. Our time is up and thanks for listening.

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