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The Four-Hit Model of IgA Nephropathy Pathogenesis

Announcer:
Welcome to ReachMD. This medical industry feature, titled "The Four-Hit Model of IgA Nephropathy Pathogenesis," is sponsored by Novartis Pharmaceuticals Corporation. Here's Dr Jai Radhakrishnan.

Dr Radhakrishnan:
Hello, my name is Dr Jai Radhakrishnan and I am a nephrologist at Columbia University Medical Center in New York. In this video, we will discuss the four-hit model of immunoglobulin A (or IgA) nephropathy pathogenesis.

IgA nephropathy is the most common primary glomerulonephritis globally. [4,10,13,14] About 25 adults per million are affected each year worldwide.[4,14] IgA nephropathy affects younger adults (aged 20-30 years) more than older adults and distribution by sex varies geographically.[8,15] IgA nephropathy is a highly heterogeneous disease; the presentation varies from asymptomatic microscopic hematuria to a more severe course characterized by sustained proteinuria, hypertension, and, in some patients, rapid deterioration of kidney function.[4,14]

Based on data from a recent large cohort study of 2,299 adults and 140 children with IgA nephropathy conducted in the UK, 50% of patients with IgA nephropathy progressed to kidney failure within 10 to 15 years of diagnosis.[8] The most widely accepted mechanism for the pathogenesis of IgA nephropathy is referred to as the "four-hit model," which is a sequence of four events that can occur in the pathogenesis of IgA nephropathy.[15-17]

Hit 1 involves increased production of galactose-deficient IgA1 (or Gd-IgA1), which is the predominant subclass of IgA found in serum.[10,11,15] Patients with IgA nephropathy demonstrate increased circulating levels of IgA1,[17,18] which is polymeric and lacks terminal galactose moieties, or GalNAc, and galactose in its hinge region.[9] This form of IgA1 is referred to as "poorly galactosylated IgA1" or galactose-deficient IgA1. Galactose-deficient IgA1 originates in the mucosa and is produced at the mucosa-associated lymphoid tissue by antibody-secreting B cells.[9,10] The changes in O-galactosylation of the IgA1 hinge region could trigger conformational changes to the molecule and a subsequent immune response.[9]

Hit 2 involves increased production of antiglycan autoantibodies directed against galactose-deficient IgA1.[10] Autoantibodies in IgA nephropathy recognize GalNAc residues in the hinge region of galactose-deficient IgA1.[15] These specific autoantibodies can include IgG or IgA, but IgG is the predominant isotype.[15]

The increased production of autoantibodies directed against galactose-deficient IgA1 results in **Hit 3**, which is the formation of immune complexes.[10] Patients with IgA nephropathy have higher circulating levels of immune complexes compared with healthy individuals.[14] These immune complexes are pathogenic and composed of galactose-deficient IgA1 and anti-galactose-deficient IgA1 autoantibodies.[14,15] These immune complexes are inefficiently cleared from circulation, so they tend to deposit in the renal mesangium.[14]

Hit 4 involves immune complex deposition and activation of inflammatory pathways,[10] including the complement system.[16] Deposition and recognition of immune complexes by mesangial IgA receptors trigger mesangial cell proliferation, release of proinflammatory and profibrotic mediators, and podocyte damage.[9] Continued immune complex deposition and mesangial cell activation can lead to progressive glomerular injury and, potentially, kidney failure.[9] Consequently, **hits 1, 2, 3, and 4** are involved in the pathogenesis of IgA nephropathy.

In summary, the pathogenesis of IgA nephropathy is complex and involves four stages or "hits".[15-17] Thank you for your time and interest in this video.

Announcer:
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