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

Unraveling IgA Nephropathy Pathogenesis: APRIL and the Four-Hit Cascade

ReachMD Announcer:
Welcome to ReachMD. This medical industry feature, titled "Unraveling IgA Nephropathy Pathogenesis: APRIL and the Four-Hit Cascade," is sponsored by Otsuka. Your host is Dr. Jennifer Caudle.

Dr. Caudle:
This is ReachMD, and I'm your host, Dr. Jennifer Caudle. And today, as part of our two-episode program focusing on IgA nephropathy, we're diving into the mechanism of disease—specifically, the four-hit cascade and the role of A Proliferation-Inducing Ligand, which is also known as APRIL, in its pathogenesis.

And joining me in this discussion are Dr. Sayna Norouzi and Dr. Jared Hassler. Dr. Norouzi is an Assistant Professor of Medicine and the Director of the Glomerular Diseases Clinic at Loma Linda University. Dr. Norouzi, thank you so much for being here today.

Dr. Norouzi:
Thank you so much for having me.

Dr. Caudle:
And Dr. Hassler is Associate Professor of Pathology and Laboratory Medicine at Temple University's Lewis Katz School of Medicine in Philadelphia. Dr. Hassler, it's great to have you with us as well.

Dr. Hassler:
It's great to be here. Thank you for the invitation.

Dr. Caudle:
Of course.

So if we start with you, Dr. Norouzi, can you give us an overview of IgA nephropathy?

Dr. Norouzi:
Sure, of course. IgA nephropathy is a progressive chronic autoimmune kidney disease.[1,2] It's caused by the deposition of immune complexes, specifically those involving galactose-deficient IgA, in the kidneys which can result in inflammation.[3] This inflammation can then cause damage to glomeruli within the kidneys, leading to clinical manifestations that we see in patients with IgA nephropathy which can include microscopic hematuria, gross hematuria, proteinuria, and ultimately leading to loss of kidney function.[4]

Dr. Norouzi:
Now in terms of prevalence, IgA nephropathy is the most common form of biopsy-proven primary glomerulonephritis globally as a leading cause of chronic kidney disease and end-stage kidney disease.[5,6] In the United States alone, the prevalence of IgA nephropathy is estimated to exceed 110,000 people and can significantly impact their quality of life due to pain, fatigue, poor mental health, and a high indirect caregiver burden.[7,8]

IgA nephropathy is typically diagnosed in individuals between the ages of 20 and 40, with many of these patients progressing to end-stage kidney disease, requiring dialysis or kidney transplant within 10 to 15 years of diagnosis based on an observational study from the UK called the RaDar study.[9–11] And alarmingly, patients undergoing dialysis or who have received transplant have a life expectancy of an average of six years shorter than the general population.[12]

And so this stark statistic underscores the urgent need for early diagnosis and intervention and also effective treatment strategies that target the pathophysiology of the disease.

Dr. Caudle:
Well, speaking of early diagnosis, let's turn to you now, Dr. Hassler. Can you explain what you see under the microscope when diagnosing IgA nephropathy and how the histopathology could relate to the disease's underlying mechanisms?

Dr. Hassler:
Certainly. Diagnosing IgA nephropathy requires a kidney biopsy, which we then analyze using different microscopic techniques: such as light microscopy, immunofluorescent microscopy, and electron microscopy.[13,14] For an IgA nephropathy diagnosis, the biopsy will reveal IgA deposits within the glomerular mesangium.[14] The histologic features of IgA nephropathy are classified by the Oxford Classification MEST-C score.[15] And it's important to note here that these histopathology scores have predictive value that's independent of clinical factors and that they've been shown to correlate with clinical outcomes.[4]

So with that being said, let's take a closer look at the histopathological lesions that make up the Oxford Classification for the MEST-C score. Within the score, we have the individual M, E, and C scores which are going to describe active inflammatory processes that we hope to improve with treatment, whereas the S and the T scores describe more chronic changes.[16]

Dr. Hassler:
Starting with 'M,' which stands for mesangial hypercellularity: if more than half the glomeruli have more than four mesangial cells in any mesangial area of a glomerulus, then that's an M1 score. An M0 score is if that feature occurs in 50 percent or less of glomeruli.[15]

Next, the 'E' stands for endocapillary hypercellularity, which is when there's an increased number of cells within the glomerular capillary lumen. A score of E0 means there's no endocapillary hypercellularity, but if I can find that feature in even just one glomerulus, that's an E1 score.[15]

Moving to 'S,' which indicates segmental glomerulosclerosis: this involves adhesion or sclerosis that doesn't affect the entire glomerulus. Similar to the E1 score, if this isn't present in any glomeruli then it's an S0, but I can find this feature in even one glomerulus, it's an S1 score.[15]

The 'T' stands for tubular atrophy and interstitial fibrosis, and it's measured by the percentage of affected cortical area. A score of T0 is anything 25 percent or less, T1 is going to range from 26 to 50 percent of the cortical area that's affected, and anything over 50 percent is going to be a T2 score.[15,17]

Lastly, the 'C' score is also on a scale. It measures the cellular or fibrocellular crescents, which are characterized by extracapillary cell proliferation. So a C0 score is if this feature isn't present at all, a C1 score is given when less than 25 percent of glomeruli are affected, and C2 is for 25 percent or more affected glomeruli.[15]

So when I'm examining a renal biopsy under the microscope, I'll describe these changes using the MEST or MEST-C score to provide crucial information—not only for diagnosing IgA nephropathy, but also to risk stratify patients using the International IgAN Prediction Tool. By combining clinical, histopathological, demographic, and treatment variables, the tool predicts the risk of experiencing either a 50 percent decline in eGFR or progression to kidney failure within up to 80 months from the kidney biopsy. And these insights on prognosis can potentially guide disease management.[4]

Dr. Caudle:
Thank you so much for breaking all of this down for us, Dr. Hassler. And now if we come back to you, Dr. Norouzi, can you delve into the causes and etiologic factors of IgA nephropathy?

Dr. Norouzi:
Sure, of course., IgA nephropathy can develop from a number of factors such as genetics and environmental, which can result in immune dysregulation of cells in the mucosa that then leads to the overproduction of IgA.[18–22] In addition, secondary causes can include IgA vasculitis or IgA nephropathy due to viral infection, inflammatory bowel disease, autoimmune disease, and liver disease.[18,23] So it's important to assess for secondary causes once the diagnosis is confirmed through the biopsy.[13]

Dr. Caudle:
Thank you. And now if we switch gears a bit and zero in on APRIL, Dr. Hassler, what is its role in the pathogenesis of IgA nephropathy?

Dr. Hassler:
Well, APRIL and B-cell activating factor, or BAFF, are cytokines and members of the tumor necrosis factor ligand superfamily, and they each play distinct roles in B-cell development. BAFF is involved in earlier stages of B-cell maturation, whereas APRIL is particularly involved in plasma cell survival and antibody switching in later stages.[1,24,25] APRIL also plays an important role in stimulating B-cells in the production of IgA and pathogenic IgA1, known as galactose-deficient or Gd-IgA1, which is implicated in IgA nephropathy.[25]

So as a result, APRIL has emerged as playing an important role in the pathogenesis of IgA nephropathy.[24] In fact, compared to those without the disease, patients with IgA nephropathy have higher serum APRIL levels. And among patients with IgA nephropathy, higher APRIL levels are associated with risk of a more rapid progression to end stage kidney disease.[26,27]

Dr. Caudle:
For those of you who are just tuning in, you're listening to ReachMD. I'm your host, Dr. Jennifer Caudle, and today I'm speaking with Drs. Sayna Norouzi and Jared Hassler about the pathophysiology of IgA nephropathy.

Thank you. And coming back to you now, Dr. Norouzi, can you explain the four-hit cascade that leads to the pathogenesis of IgA nephropathy and how APRIL is involved?

Dr. Norouzi:
So the four-hit cascade is the pathophysiological process that leads to renal injury and disease progression in the setting of IgA nephropathy.[3]

Let's start with APRIL, which is produced in the mucosa, and as we discussed: supports the development of B-cell lymphocytes and promotes the class-switching of B cells, and also stimulates plasma cells to produce IgA and Galactose deficient-IgA1.[1,24,25]

1. In Hit 1, we see enhanced production of Galactose deficient-IgA1 production due to an abnormal immune response in the mucosa.[18]
2. Then, in Hit 2, the circulating Galactose deficient-IgA1 acts as an autoantigen, triggering an immune response which leads to the synthesis of anti-Galactose deficient-IgA1 autoantibodies. These high levels of autoantibodies directed against Galactose deficient-IgA1 which correlates with IgA nephropathy disease severity.[3,18]
3. Next, in Hit 3, we see the formation of large pathogenic immune complexes as a result of these autoantibodies binding to Galactose deficient-IgA1.[18,28]
4. And finally, in Hit 4, these immune complexes deposit in the mesangium of the glomerulus. There, they activate mesangial cells and the complement system, augmenting the inflammatory cascade, and in return, causing renal injury and inflammation.[3,18] APRIL, through its continued support of plasma cell survival and autoantibody production, perpetuates this cycle, leading to chronic inflammation and renal damage.[24]

And so, by understanding the role of APRIL in this cascade, we can see how it's a sustaining factor in the pathogenesis of IgA nephropathy.

Dr. Caudle:
That's very interesting. And now, Dr. Hassler, how does this cascade correlate with findings on the kidney biopsy?

Dr. Hassler:
The elevated levels of Gd-IgA1 and autoantibodies directed against Gd-IgA1 lead to the formation of immune complexes that deposit into the mesangium of the glomerulus, manifesting an inflammatory response that can result in mesangial and endocapillary proliferation on renal biopsy.[15,18]

And once this inflammatory cascade starts, and the mesangium begins to expand, multiple processes can damage the glomerular basement membranes as well. This basement membrane injury is where the proteinuria, and potentially the hematuria, can come from, and leads to the scarring in the tubular interstitium that we see in the disease.[5,15]

So on a tissue level, the damage from the deposition of immune complexes is what's classified with the MEST-C score, and the severity that we see on biopsy correlates with IgA nephropathy disease severity.[3,15]

Dr. Caudle:
And if we stick with you for just another moment, Dr. Hassler, are there any other pathways involved in IgA nephropathy?

Dr. Hassler:

Yes, there are a variety of other pathogenic mechanisms at play. For example, the complement pathway is activated during Hit 4 of the pathogenic cascade as it responds to the deposition of immune complexes within the kidney.[29,30] The endothelin pathway is another mechanism that's activated during Hit 4, further contributing to the inflammatory response and renal injury.[1,31,32]

Dr. Caudle:
And with that in mind, Dr. Norouzi, what are the clinical manifestations of IgA nephropathy and the drug classes that target these hits?

Dr. Norouzi:
The clinical manifestations of IgA nephropathy include increased proteinuria, hematuria, and reduced kidney function, and various drug classes target different steps of the four-hit cascade.[30,33,34]

For instance, drug classes that reduce pathogenic IgA1, as well as the autoantibodies against pathogenic IgA1, such as APRIL inhibitors and APRIL/BAFF inhibitors, can act prior to the initiation of the 4-HIT cascade, as well as on Hit 1 and Hit 2, leading to the reduced production of Galactose deficient-IgA1.[30,34]

Other classes reduce the glomerular inflammation from Hit 4, such as complement inhibitors.[34]

And lastly, various drug classes are meant to address generic CKD drivers of continued nephron loss, such as RAAS inhibitors, SGLT2 inhibitors, and endothelin receptor antagonists.[34]

Dr. Caudle:
So then before we close, Dr. Hassler, can you tell us why targeting APRIL could be a potential therapeutic strategy for IgA nephropathy?

Dr. Hassler:
Sure, targeting APRIL is important because the literature suggests it plays a key role in the pathogenesis of IgA nephropathy.[1,24,25] Evidence also suggests that blocking APRIL may reduce the production of Gd-IgA1, as well as anti-Gd-IgA1 autoantibodies, decreasing the formation and deposition of the pathogenic immune complexes in the mesangium.[35,36] And so my colleagues and I are interested in whether this targeted approach has the potential to mitigate renal injury and perhaps even delay the onset of end stage kidney disease. Because at the end of the day, there's still a need for agents that precisely target the underlying pathophysiology of IgA nephropathy.[9,37]

Dr. Caudle:
Thank you both for such an informative discussion today on IgA nephropathy. And as that brings us to the end of the first episode of our two-part program, I'd like to thank my guests, Drs. Sayna Norouzi and Jared Hassler, for joining me to talk about the pathophysiology of IgA nephropathy, the role of APRIL, and the four-hit cascade. Dr. Norouzi and Dr. Hassler, it was great speaking with you both today!

Dr. Hassler:
Thank you for having us.

Dr. Norouzi:
Sure of course. It was a pleasure to be here.

Dr. Caudle:
And for ReachMD, I'm your host, Dr. Jennifer Caudle. And if you'd like to learn more about disease progression and the urgency for early intervention for IgA nephropathy, please stay tuned for our next episode in this two-part program. Thank you, and we'll see you next time!

ReachMD Announcer:
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