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AMKD pathophysiology: What We Currently Know

Announcer:
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Dr. Hung:
Hi my name is Adriana Hung, and I am Associate Professor of Medicine in Nephrology at the Vanderbilt University. The topic that we will present today is APOL1-mediated kidney disease pathophysiology.

The first time that it was identified that the risk variants in the APOL1 were associated with kidney disease was in the context of HIV-associated nephropathy, or also known as HIVAN. Actually, HIVAN is most severe form of APOL1-mediated kidney disease. This was discovered by Jeffrey Kopp and Cheryl Winkler, who using mixture mapping were able to delineate an area in the chromosome 22 that was associated with HIVAN and idiopathic FSGS. Two years later, Martin Pollak's group, using point mapping, were able to identify that those variants were located in the APOL1 gene and identify G1 and G2.

Having high-risk variants is a common condition in individuals of African ancestry. This data that I'm presenting here is for the Million Veteran Program, currently the largest biobank and more diverse biobank in the world. This data comes from 121,000 individuals across the nation. And we have that the prevalence of two high-risk variants is 12.9%. This is highly accurate in concordance with what's been observed in older cohorts. Now, if you go to your renal clinic, that prevalence will be significantly higher. For example, here in NEPTUNE, which is study of nephrotic syndrome in kids, that prevalence can be up to 47%.

But now not everybody that has a high-risk genotype will develop kidney disease. And because of that, we handle the second hit hypothesis. That means that gene environment and gene-gene interactions play a key role in the development of APOL1-mediated kidney disease. So for environmental interactions, I'm going to

use these figures put together by Juan Carlos Velez, presented in the Nature Reviews Nephrology, which is highly comprehensive in the pathophysiology of the process. And we can observe how for example, HIV, Parvovirus B and 19, and also (inaudible) generates AMKD. So, these conditions have in common that they increase significantly the release of cytokines, particularly of interferon. And interferon will increase the gene expression of APOL1 in the podocytes, and create podocyte proliferation and podocyte de-differentiation in crowding of the glomerular space, that then will generate the occurrence of a pseudo-crescent.

As you can see here, this particular histology is from somebody with HIVAN, and you can also observe here in the electron microscope in the occurrence of a tubulo-reticular inclusion body, also known as interferon footprint. This is not (inaudible) of APOL1; it just means that this pathophysiology being observed is associated or mediated by a highly inflammatory process with high levels of interferon.

Now, during the COVID-19 epidemic, we learned that the incidence rate for AKI was high. So in different studies, it was described anywhere from 30 to 50%. I chose to chair this particular study because it's a national cohort of 5,216 individuals. And then they highlighted that individuals of black race had a odds ratio of 1.9 and the risk of developing AKI, and had a much higher risk of dying. And

so, we decided that it was important to study if APOL1 was mediated that disparity, so we evaluated if APOL1 had to do with the risk of AKI and death in individuals of African ancestry if needed with COVID-19. And we used the Million Veteran Program. And we did observe that if you had a high-risk genotype, that risk was 51%, compared to 30.9% individuals of low-risk genotypes. So these provide a very important messages, including that you had the opportunity to apply personalized care. For example, you cannot administer interferons to individuals with the potential of having an APOL1 high-risk genotype, that anti-inflammatories may have a higher efficacy.

In the future, as they are several APOL1 blockers in the pipeline's when they become available, this may be the medication of choice, and that this

pathophysiology may not be just limited to the COVID-19 context, but may be extended to other high inflammatory or critically ill patients.

When we highlighted studies by Katalin Susztak have now shown too that it's not just (inaudible) but there's also an endothelial phenotype that is activated by the NLRP inflammasome. In that particular association, it was reproduced in MVP as shown in association of high-risk genotypes in APOL1 with sepsis and sepsis-related conditions.

I want to highlight that there are other important and many other important environmental factors, but I'm just going to mention hypertension is being shown that high-risk APOL1 genotype is associated with early hypertension and more severe hypertension. This is important because it provides an opportunity to intervene earlier.

Moving to gene-gene interactions, this could be outside the APOL1 gene for sure. Just shown an example of a gene-gene interaction with other risk variants within the same APOL1 gene, we have been focusing on G1 and G2, but there may be many other variants in the APOL1, as I said. And so the question is, if this happened in the context of other barriers, what will happen to the nephrotoxicity of G1 and G2 In vitro studies by Herbert Lannon have shown that it could change and modify the nephrotoxicity. And so we did look at these in the Million Veteran Program in humans, and we were able to show that individuals with high-risk genotype with other - lacking other variants had a tremendous risk of developing ESKV which is in red. But if they had other APOL1 variants like the N264K, in blue, that could be protected. And so gene-gene interactions are very important to understand for toxicity of G1 and G2. And that is through the inhibition of the pore performing of G1 and G2.

Finally, I just want to mention that there's been many different mechanisms that are described for nephrotoxicity associated to APOL1 risk variants, but these are the four that have been agreed upon the most. That is, the pore formation on the cell membrane that functions as ion channel then produces cell swelling in lysis, pore formation in the inner mitochondrial membrane, misfolding of the ER and causing ER stress, the interaction with the cytoskeleton which produces proliferation in the de-differentiation of the podocyte. And I just want to highlight that the one that's been targeted by most mitigations or interventions right now is a pore formation.

And so in summary, APOL1 high-risk genotypes are common. They explain a significant proportion of the accessories that we see in individuals of African ancestry, but not everybody will develop kidney disease. So it's important to understand who will develop kidney disease in order to decide who we need to genotype and who we do need to intervene in. So other studies with longitudinal data and important to understand more environment and other genes that will interact with G1 and G2, and increase the risk of AMKD. And so, just want to thank you all for listening.

Announcer:
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