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Optimizing the Care and Quality of Life for Patients with ADPKD – Part 2: Progression and Prognostication

Announcer Opening:
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DR. DAHL:
Hello and welcome to this webcast titled, Optimizing the Care for Patients with ADPKD. This is part two of four in our CME series on Improving the Care and Quality of Life for Patients with Autosomal Dominant Polycystic Kidney Disease, or ADPKD. In this webcast, we'll focus on disease state progression and prognostication.

I am Dr. Neera Dahl, an Associate Professor of Medicine at the Yale University School of Medicine. And I'm joined today by my colleague, Dr. Matthew Lanktree of McMaster University. Dr. Lanktree, please introduce yourself.

DR. LANKTREE:
Thanks, Neera. Uh, my name is Matt Lanktree. I'm a nephrologist and geneticist at McMaster University in Hamilton, Ontario, Canada, and I have a special interest in, uh, treating patients with ADPKD. And I'm really excited to talk about it today with you.

DR. DAHL:
Excellent. We’re very glad that you're here.

Now let's review the learning objectives for this webcast. Upon its conclusion, participants should be able to recognize tools and resources, including the male classification system based on imaging to monitor disease progression, describe the relationship between total kidney volume, calculated GFR, and the age for detecting rapid progressors, and applying the PROPKD scoring system to predict renal survival in ADPKD.

And I'd like to start us off by presenting a case. So this is a young man with ADPKD. His father developed end-stage kidney disease at the age of 49. The patient developed high blood pressure at the age of 21. And his blood pressure is now well controlled on an angiotensin receptor blocker. He has a creatine of 1 and a bland urinalysis. And what we're seeing here is an image of his kidney by ultrasound. And what you see is that his kidneys are cystic and the cysts uniform throughout the kidney. And by ultrasound measurements, we know that the kidneys are large, one is 16.5 centimeters, and the other is 17 centimeters. This shows the, uh, coronal image of a - a coronal MRI image of his kidneys, and here I'm showing you the kidney volumes. The right kidney is 530 mL, the left is 594. And his height adjusted total kidney volume is 661 mils per meter. And this is consistent given his age with a Mayo classification of 1E.

And just to compare the two different prognostic systems we'll see is Mayo Imaging classification is 1E, versus if he had a truncating PKD-1 mutation, and we'll talk about what that means, his is PROPKD score is 9. So by both classifications, he's at high risk of progressive loss of renal function.

We can contrast this to someone who is a slow progressor. So this is a 45-year-old woman. She developed high blood pressure in her early 40s. She has a Mayo Imaging classification of IB and has normal renal function. Matt, how do you go about defining who would be a rapid progressor?

DR. LANKTREE:
Thanks, Neera. I think it's important that we recognize that the rate of progression can vary greatly among patients who all have ADPKD. So while some patients will develop kidney failure in the fourth decade of life, some it will be delayed even into the seventh decade of life. And so risk stratification is the most important part of, uh, identifying the patients that require more aggressive treatment.

So those with rapid progression are more likely to have early hypertension, to have early urological complications, usually gross hematuria episodes, they have larger kidneys that grow at a faster rate, and they have faster declines of their estimated GFR. And so all of these features can be useful in identifying the patients that have more rapid disease. And of course, the underlying mutation type contributes to these, uh, features that we can see in our patients and others. And all together, this can be used to stratify patients. Neera, so can you maybe go over what the Mayo Clinic classification is?

DR. DAHL:
That would be my pleasure. So the Mayo Imaging classification is a mechanism by which we can use kidney measurements to determine patient's risk of progression. So this is a, um, the, uh, slide that shows what some of those inputs are for de - determining the Mayo Imaging Class. So what you see here is we're looking for kidney measurements of the right and left kidney, the – the length, the width, and the depth. And with that, uh, um, uh, there's a total kidney volume that is calculated by adding the kidney volumes of the right and left kidney together. And then based on that, and based on the patient's age, a imaging classification score is derived.

It's important to remember that the Mayo Imaging classification tool should be used for people who have bilaterally enlarged, symmetric kidneys. Someone who has, uh, very lopsided kidneys or cysts maybe in one kidney and not in the other would not be eligible for this classification tool.

The tool then divides patients into these five classes. Class 1A is at lowest risk of progression versus class 1E is at the highest risk of progression. Patients tend to remain in their classification curve, meaning someone who is, uh, a rapid progressor, such as a 1E patient, tends to have rapidly enlarging kidneys, where someone who's at low risk of progression such as a 1A patient, tends to have a much lower rate of enlargement of kidney volume.

The reason the rate of enlargement is important is it also correlates to the rate of loss of kidney function. So we know in ADPKD, that there's an increase in kidney size well before the onset of loss of kidney function. But we know that the people who are growing in – in terms of kidney size, the most rapidly are also those patients who will lose kidney function most rapidly.

And now shown nicely on this slide where they demonstrated who is in the class A versus class E. And then now looking at the age of onset of loss of kidney function. So you can see that the class A patients may have fairly normal kidney disease until their fifth decade versus the class E patients will start to have a decline in kidney function by their third decade. Matt, how does genetic testing fit into risk classification?

DR. LANKTREE:
Thanks, Neera. So the Mayo Clinic classification explains the biggest proportion of variability in risk. But genetics can be especially helpful in cases where the diagnosis is somewhat in question. So people may be familiar with the Ravine-Pei criteria for diagnosis of ADPKD, which relies on having a positive family history. If there's no apparent family history, the pretest probability of having ADPKD falls from 50% in the context of those with a family history to 1 in 1,000, the population prevalence of ADPKD. So genetic testing can be particularly helpful in locking a diagnosis in a patient with a causal mutation without a family history.

Additionally, if you need to make a diagnosis in a young patient, where the Mayo Clinic classes are very close together, um, genetics can be helpful in those early cases. In prenatal or pre-implantation genetic diagnostics, again, genetic testing can identify whether the disease will be present before it manifests. If there's a large degree of phenotype discordance, so one family member has very severe early onset disease and another family member as milder, uh, relatively smaller and slower loss of EGFR, potentially genetic testing can identify if there's another, uh, digenic, or genetic contributor to the more severe phenotype. If there's a question of a possible syndromic form of cystic kidney disease where people have other extra renal manifests have something like nephronophthisis, then potentially genetic testing could be helpful.

And finally, in the situation of atypical imaging where there isn't a bilateral uniform cyst distribution, genetic testing can help make that diagnosis. The French group in the Genkyst cohort, were the first to develop something called the PROPKD score. And so they recognized that the patients with the highest risk of progression had early hypertension, had early urologic events, they recognized there was more rapid progression in males than in females, and they described the relationship between PKD-2 mutations, the more severe PKD-1, and then differentiating those with non-truncating versus truncating mutations. So together, the PROPKD score adds together point for being male, two points for early hypertension, two points for early urologic events, and then zero, two, or four points for the underlying mutation type.

Here you can see the distribution of renal survival based on your underlying low, intermediate, or high risk PKD score. However, it's important to remember that there's a distribution of people with these risk scores. In the Toronto cohort, we evaluated the people who had the most severe protein truncating PKD-1 mutations, but still see a distribution at the age of kidney failure. A fifth of patients had low risk Mayo Clinic classifications, even though they had severe mutation types, and the age had kidney failure, a fifth of patients still develop kidney failure after the age of 65.

So this is important to understand that while the mutation type does contribute to prognosis, there's still substantial phenotypic heterogeneity even in people with the same mutation class.

So Neera, can you talk about how some of the environmental factors add into genetic factors to determine the rate of disease progression in PKD?

DR. DAHL:
I'd be happy to do that. And I think, Matt, just to finish the thought in terms of the genetic information you showed us, it really points to the reason to consider doing the Mayo Imaging classification as a way of really predicting risk of progression over perhaps a – a genetic score.

But here, uh, what we're showing you is what are some of those different genetic versus epigenetic versus clinical factors that could lead to risk of progression. So we've talked about the genetics, we talked about the early presentation of hypertension or urologic event, and imaging classification. The environmental factors that are very important include fluid intake with low fluid intake being a risk factor for progression, salt intake with high salt intake being a risk for progression, high caloric intake, and there's a lot of focus on - on how that impacts ADPKD now, and a high BMI. So we know that all of those things can increase risk of progression. In addition, there are some biomarkers that we may follow. So obviously, we'll follow how quickly GFR is declining. But there is some role in looking at proteinuria or albuminuria, and then some role in looking at some of these other biomarkers as well.

And this, I think, is a slide that really links the two things we've been talking about together. So list the imaging, uh, classification with the genetic score. And what you see here are, uh, the, um, the Mayo Imaging classification on the bottom. So 1A, which is the milder disease to 1E which is the more severe disease. And on the top, what you see are the - the genotype that are associated with that particular score. So you can see that PKD-2 patients tend to be over-represented in the group that have the 1A or the 1B imaging classification, versus patients who are 1E tend to have more of the PKD-1 truncating mutations.

And to bring this back to our patient, our patient was at high risk of progression because of his family history, because of his early onset of hypertension, and because of his large kidneys. So an ultrasound measurement of great - greater than 16.5 in a young patient is consistent with a high risk of progression, but also his imaging classification was 1E. And although I don't have his genotype, assuming that he has a truncating PKD-1 mutation, his PROPKD score would be 9.

In summary, it's important to determine whether a patient is a rapid progressor or a non-rapid progressor. And total kidney volume is the most important biomarker for determining this. Tools such as the Mayo classification and PROPKD score are used to stratify patients and optimize care.

And here's a pictorial, um, summary of what we've been talking about. So this is looking at EGFR or kidney function on the X axis, and on the Y axis, you see total kidney volume or cyst number.

So we know in ADPKD, that we are worried about the patients who have very large kidneys. And those patients, um, can be identified as being at high risk, even before they have significant loss of renal function. And that's really our job as clinicians is to try and identify those patients who are at high risk of progression before they have had significant loss of renal function. And that's to compare people who maybe are at lower risk of progression and will always have fairly normal kidney function.

Matt, how would you summarize this information?

DR. LANKTREE:
Thanks, Neera. Here is an approach to risk stratification of patients with ADPKD. Patients with renal cysts should first be evaluated to confirm the presence of an ADPKD diagnosis. in the context of a positive family history and typical imaging features, that is sufficient to confirm the diagnosis. If there's atypical features, perhaps the lack of extra renal manifestations, uh, atypical imaging patterns, or a lack of family history, genetic testing can be useful to help clinch the diagnosis.

As Neera's described, the Mayo Clinic Imaging classification explains the most variability of risk progression, and is very useful in differentiating those at high versus low risk, especially in the middle of the distribution. Those with Mayo class 1C, 1D, or 1E, are at risk of rapid progression, and are needing, uh, aggressive therapy. Patients with Mayo class 1A, 1B, or atypical imaging features we know are at a low risk of progression to advanced stages of CKD. And thus can be treated with more conservative measures.

DR. DAHL:
Matt, we just spent the last 20 minutes or so talking about progression and prognostication in ADPKD. I think often people get confused about the variability of expression of disease within a family. Could you talk to us about that?

DR. LANKTREE:
In the Toronto cohort, we looked at how often family members had kidney failure at the same age, because family members have the same underlying mutation. If the disease was purely driven by the mutation alone, you would expect family members with the same mutation to have the same age of kidney failure. Two thirds of family members had kidney failure within six years of each other. So clearly, the underlying mutation is important. However, we still found a – a third of families that had discordance in their phenotype, and some that had even varied discording. So one family member had kidney failure before age 55 and another family member had kidney failure past age 70.

So clearly, there is other things, environmental or additional genetic factors, that contribute to variability in disease severity beyond the germline or the main effects mutation. People often think about penetrance as being either black or white, complete or incomplete. Meaning that if you have the mutation, a fully penetrant mutation, everybody should have the disease and incomplete penetrance meaning that if you have the mutation, maybe some people don't have the disease at all. It's important to contrast this with variable expressivity, recognizing that instead of a discrete toggle switch, it's actually more of a volume knob. And people can go from white to gray to black and all of the shades in between.

And so, in the Toronto group, we didn't find any patients with the most severe protein truncating PKD-1 mutations who had no cysts at all. So there's a very high sensitivity for disease, if you have a PKD-1 mutation. If you have the mutation, you're gonna have cysts. But at the same time, there's still variable expressivity, with some people having very severe disease and some people having relatively mild disease while still having that same mutation type.

So this gets to the difference between diagnosis and prognosis, using genetics in ADPKD. So imaging later in life can evaluate your current phenotype, which includes all of the environmental exposures that have happened throughout your life. Genetics, on the other hand, stays the same throughout your whole life. So that's very useful if we want to make a diagnosis at a young age before we've even been exposed to the things in our life. So both genetics and imaging have important roles for diagnosis and for prognostication, but they have strengths and benefits at different times throughout our life.

DR. DAHL:
Matt, thanks very much for that very nice explanation.

DR. LANKTREE:
Thanks for the question. And I - I hope people found it interesting.

DR. DAHL:
Dr. Lanktree, thank you very much for going through this information with us.

I'd like to thank all of the listeners and all of the participants, and I hope you have enjoyed this session. I hope you'll take advantage of the other sessions in this module and have a look at them as well.

DR. LANKTREE:
Thanks, Neera. It's been a lot of fun. Thank you everyone for your attention. I'm always excited to talk about ADPKD, and I'm going to check out those other modules myself.

Announcer Closing:
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