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Prognostic Tools in the Management of ADPKD

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Dr. Park:
Hello, and welcome to this webcast titled "Prognostic Tools in the Management of ADPKD." My name is Meyeon Park, and I'm Associate Professor of Medicine at the University of California, San Francisco, and Director of the PKD Center of Excellence. I'm joined today by my colleague, Dr. Anjay Rastogi. Dr. Rastogi, please introduce yourself.

Dr. Rastogi:
Thank you, Dr. Park. As Dr. Park mentioned, my name is Anjay Rastogi. I'm a nephrologist at UCLA Professor of Medicine, and also the Director of the UCLA CORE Kidney Program. That includes the PKD program, and it's a real pleasure to be here, Dr. Park.

Dr. Park:
Same here. Before we get started, let's review our learning objectives. Upon conclusion of this educational activity, participants should be able to recognize tools and resources, including imaging studies and the Mayo Clinic classification system to assess risk of disease progression, describe the relationship between total kidney volume, estimated GFR, and age for detecting rapid progressors, and consider other factors that contribute to disease severity or risk of disease progression in ADPKD.

Dr. Rastogi:
So with that, Dr. Park, I'll be going over the total kidney volume and other factors that help predicting progression of kidney disease in ADPKD.

So let's start with the diagnosis. When we look at ADPKD. It has very close ties with radiology and imaging. And one of the key tools used to diagnose ADPKD is an imaging test. It could be an ultrasound, it could be a CT scan, it could be an MRI. But ultrasound is the one that's most frequently used. And based on your age and number of cysts, if you have a positive family history of ADPKD, the diagnosis can be made.

Now in case there is no family history of ADPKD or if the imaging test is inconclusive, in that case, we actually go to genetic testing. Now, in the past, gene testing was unaffordable, inaccessible. But we have made significant progress, I will say over the last 10 years. And it's now is actually much more accessible, and we do it quite frequently at UCLA.

Dr. Park, how about you, gene testing it at UCSF?

Dr. Park:
There's definitely situations where we use genetic testing. Most of the time, we'll start with other modalities for diagnosing and working

up patients and considering their risk, but occasionally genetic testing can be very helpful.

Dr. Rastogi:
Great. Now, imaging like I said, the ties between radiology and ADPKD are very strong for diagnostic. The question is, is it more than just diagnostic? Can we use imaging for prognostic purposes? And we'll be going over that in a lot more detail today.

Now just going over the pathogenesis of ADPKD. ADPKD, as the name implies, is autosomal dominant polycystic kidney disease and it's caused by mutations in two of the genes; one is on chromosome 16, one is on chromosome 4, type 1 and type 2. But what's interesting is only 10% of the nephrons are actually affected, even though it's a genetic disease, 90% of the other nephrons, quote unquote, don't have the mutation. The cysts grow over time. There's both fluid secretion as well as cellular proliferation that contribute to the cyst growth. And over time, these cysts, which are bilaterally symmetrical, diffuse, they will destroy the tissue architecture, and that leads to kidney dysfunction.

But as you can see in this slide, the - and I mentioned that 90% of the nephrons are, quote unquote, normal and they tend to hyper-filter for the 10% defective nephrons. So initially, the kidney function as measured by GFR is maintained, quote unquote, within the normal range till we hit the cliff and then the GFR starts going down. But in this time when the GFR is being maintained normal by hyper-filtering nephrons, the kidneys tend to still grow. So in this early stage, the kidney size is a better predictor of disease progression than simple blood test with GFR.

Now there's lots of variability even though they – you might have the mutation. You have the diagnosis of ADPKD, there is variability in disease progression, and within sometimes within the same family. And the question comes out, can we predict which patients are going to be progressing more rapidly than others? And why is that important? Well, it's important for the patient, what they want to know, first of all, what is their prognosis, they also want to plan their life, they want to plan their family. But in a more treatment portion, they might be eligible for treatments that are applicable for patients who are rapid progressors light tolvaptan.

And last but not the least, we should not forget about clinical trials. The enriched population, we want to look at these patients who tend to be rapid progressors, and they enroll in these studies.

So in this next slide, we'll be looking at some of the factors that actually can predict which patients are rapid progressors versus others, which might not progress that rapidly. So these are the five grade buckets. The one right at the top is the clinical predictors, and this includes hypertension, urological issues, including gross hematuria, and early decrease in GFR. Then we also have laboratory predictors, and that includes proteinuria, microalbuminuria, and elevated copeptin. Genetic predictors, it is a genetic disease. And if it - depending upon we have type 1 versus type 2. And even in the mutation, whether it's truncating, or non-truncating mutations, these things can affect the prognosis of the patient. Then we have imaging predictors, which we'll be going over in a lot more detail. And then a term that we'll be using quite frequently throughout the rest of the presentation is TKV, which stands for total kidney volume. And then finally, on the left-hand side, we have the environmental factors that include your diet and your lifestyle, and don't forget smoking.

Now let's go over TKV, total kidney volume. That's a term that we as nephrologists, especially nephrologists who focus on ADPKD, use quite frequently. When I was a fellow, we would look at the longest dimension of the kidney, 10 centimeters, 12 centimeters, 18 centimeters. But now we know that doesn't give the full picture. What gives the full picture is the 3-dimensional, the TKV. So the length, the width, the depth. And that is actually included when we calculate TKV based on the imaging study. And studies have shown TKV, especially in the early stages, like I mentioned, when GFR is maintained by the hyper-filtering normal nephrons, TKV is a much better predictor of progression of disease. MRI and CT scans are the better modalities to do the imaging. But if those are not available, for whatever reason, we can also do ultrasounds.

Now let's do a bit more deeper dive into imaging. And the one that we use quite frequently is came from Mayo Clinic. It's called the Mayo Clinic Imaging Classification for ADPKD. And it's a relatively simple tool. All that you need to have is the TVK, which we'll be going over. You need the height, so it's height adjusted, and the age. And you plot these numbers on this table and you will get five prognostic classes, class 1A, 1B, 1C, 1D, 1E; 1A is the slowest progressing, 1B is mid or moderate, and 1C, 1D, 1E are what I call the rapid progressors.

And this is another way to look at it. As you can see on the top, on the Y axis you have height-adjusted TKV in mils per meter. And on the X axis you have the patient's age in years. And you can go over any numbers you have 1A, 1B, 1C, 1D, 1E, and they represent the rate of growth. And to give some idea, 1A would be 1.5% or below and then it goes to 1.5 to 3, 3 to 4.5, 4.5 to 6, and 1E, which is the most rapid progressors, is above 6% growth per year. And for theoretical purposes, the height-adjusted TKV of 150 mils per meter is considered the baseline.

On the bottom side, on the graph, you can see the EGFR prediction and when will these patients predict based on this model, would end up with ESKD. And once again, as you can see, the class 1A is the least progressive. And 1E is the most rapid progressive of these

five prognostic classes.

There's another tool that is used. We don't use it that often, at least in our practice, but it's called PROPKD. And the variables that we use for this scoring system is number one is gender, male versus female. Males have worse prognosis and they get 1 point. If you're hypertensive before the age of 35, if you are, you get 2 points; if you're not, then you are going to get zero point. If you have a urological event before the age 35, which could include hematuria, you get 2 points; if you don't have it, get zero. And then find the mutation. If you have type 1 mutation versus type 2, and if it's type 1 mutation, is it truncating or non-truncating. And then they, based on the scoring zero to 3 are low, 4 to 6 are moderate, and 7 to 9 are what we call rapid progressive. These patients will - and you can look at the prediction when they would end up with ESKD.

So with that, Dr. Park, if you can discuss your practice at UCSF as well, between Mayo Clinic Classification and also PROPKD?

Dr. Park:
Sure, we generally tend to use Mayo Classification as well. We rely heavily on the total kidney volume, as you mentioned. But what I think is interesting and convenient about the PROPKD score, even in the absence of definitive genetic testing results, is that you can use it quickly when evaluating patient to consider if the patient has had any clinical features that may raise your suspicion for risk of rapid progression.

And then on top of that, if you do have access to a genotype, you can add that into the score to improve risk prediction. But what's interesting about the genotype is that actually, it turns out to be imaging predominantly that predicts progression. And as this figure shows, there can be considerable overlap in the Mayo Classification as described by classes A through E, as you described, and the genotype. So of course, we do see that PKD2 mutations tend to be a little bit more mild, associated with classes A and B imaging features, whereas PKD1 truncating mutations tend to be more severe. But there is a middle zone where there is some overlap in this, and adding genotypic information to the imaging may improve prediction of ESKD endpoints.

Dr. Rastogi:
So now, Dr. Park, you'll be going over a practical approach in some cases?

Dr. Park:
Yes.

Dr. Rastogi:
Yeah.

Dr. Park:
Let's start with a straightforward common case. So for patient number one, this is a 24-year-old gentleman who has a family history of ADPKD. He already has a diagnosis of hypertension, experienced gross hematuria, and has abdominal fullness that he can sense and that you see on exam. Suppose his EGFR is within a normal range. Where would you start in terms of evaluating this patient? And what would you do as your first step?

Dr. Rastogi:
Yeah. So this is what we call typical bread-and-butter case, 24-year-old gentleman has a family history of ADPKD. And, you know, we went over the PROPKD, younger than 35 years, he already has hypertension, he has hematuria, it looks like his kidneys are pretty big, and even the liver could be big, he has abdominal fullness, but the EGFR is within normal range. And we discuss that as well, initially, because of the hyper-filtering nephrons, the EGFR, you know, even the kidneys might be big, might be within - and that's a bad predictor. You know, it's – and a lot of patients come in and say, 'Well, Doctor, you're telling me that I have advanced or I have big kidneys, but my kidney function is normal.' So I think these are all important.

My next test would obviously be an imaging test, preferably MRI if we can get that and getting TKV that will help us get the Mayo Clinic Classification.

Dr. Park:
So suppose we found that he had a class 1E categorization on the Mayo Imaging Classification system. How would you use this to determine the management of the patient?

Dr. Rastogi:
That's a good point. So I - you know, based on what I saw in these symptoms and history, I'm not surprised he has class 1E, which is the most rapid progressors. And if you want to throw in what kind of mutation he might have, right? If we did a gene testing, it probably would be a type 1 mutation. Now this patient will need aggressive management. He, you know, he's 24 years old, and really is progressing, he's probably going to end up with ESKD within the next 5 or 10 years.

Lifestyle modifications are always important, you know, whether it be diet, hydration, blood pressure management, but also disease-modifying therapy. Tolvaptan is the first and only drug that's approved in the U.S. to slow down progression. And this would be an ideal candidate, in my opinion, for that.

So our first case, Dr. Park, was what we call a typical case that we see in our clinic. This case number two is, quote unquote, an atypical case. So let's go over this. This is a patient 38-year-old female who presented to the ED with hypertensive emergency, and on further workup, which included some blood work, and that showed a normal EGFR. And she also had some imaging tests done. And those imaging tests were highly suggestive of ADPKD. When she was asked, does she have any family history of ADPKD, she denied having that. She was also complaining of some flank pain. And with that piece of information, this patient was then sent to you for further management. So what would we do with this 38-year-old female?

Dr. Park:
Yeah, so thank you. I think that this is a very interesting case. This is a woman who's 38, presenting with hypertensive emergency after having been healthy her whole life. Receiving this diagnosis was quite a shock to her since she had not been aware of any family history of kidney disease or kidney cysts in her family. It turned out on further probing that, indeed, her father did have bilateral kidney cysts that she had not been aware of. And she did have a family history of polycystic kidney disease, which is not an uncommon situation that we see in patients coming to clinic that it's possible that without a known family history, they actually may discover a family history with more investigation and discussion with family members.

That said, even without a family history, she met criteria for autosomal dominant polycystic kidney disease based on her initial ultrasound from the emergency department. And in order to better characterize her disease, we ordered an MRI to calculate a total kidney volume. This revealed class 1C disease, which is an intermediate-risk category, but does carry risk of rapid progression. Because of her initial concern about ambiguity of her diagnosis, since this was such a shock to her, and she had not been aware of her father's cysts on the kidneys, she did desire genetic testing, which we offered as well. And this resulted in finding a PKD2 mutation that was consistent with autosomal dominant polycystic kidney disease diagnosis.

With this information, I think that it is a little bit of a subtle discussion as to what are the optimal tools for managing her. Based on the genetic testing and the class 1C imaging characteristics, she does not clearly fall into as clear-cut of a category as our first case where it was a slam dunk that one would need to be as aggressive as possible to manage that patient. Of course, in her case, we have to optimize her hypertensive management. And I think that we could consider disease-modifying therapy with tolvaptan, even in this setting, based on the fact that we discussed before that there's overlap in imaging and genotype classes, and that even with a PKD2 mutation with 1C disease, that would indicate that there could possibly be benefit to slowing down the growth of cysts.

A recent study from Japan did show that regardless of genotype, there was an effect that was favorable measured on total kidney volume, regardless of genotype and kidney function that was obtained from tolvaptan use.

So I think that it's a little bit more of a gray zone in terms of what one might do in this case.

Dr. Rastogi:
No, I would agree completely with you, Dr. Park. And talking about the variability, there a lot of factors, and genetics is one of them. I think that always has to be kept in mind. At the end, it's a size that really, you know, the Mayo Clinic class. And once 1C does qualify as the rapid progressors, 1C, 1D, 1E. So I would agree with you completely, lifestyle modifications, all the supportive treatment, blood pressure management, and disease-modifying therapy. So that would probably be the way to go in her case.

Also, I think you mentioned, which I just want to point out about patients who don't have a family history, some of them actually do, they just don't know it. But there might be some patients that it's a de novo mutation they don't have. And that's with the gene testing, even though the imaging tests could be suggestive of ADPKD, a lot of these patients would benefit from the gene testing as well.

Dr. Park:
Yes. And I think that it's important to point out that genetic testing is also not foolproof. And sometimes we see that in 10 to 15% of cases, there's no mutation detected.

Dr. Rastogi:
Yes.

Dr. Park:
That said, I do find it to be quite useful.

Dr. Rastogi:
Right.

Dr. Park:
In this particular instance, she did feel more settled with her diagnosis, having had this conclusive evidence of known pathogenic mutation.

Dr. Rastogi:
Right. Yeah. And I think that's an important point too, because they are patients that behave as ADPKD clinically, but might not have the mutations that we test for. So that's – and PKD1 is a difficult gene to look at.

Dr. Park:
As we know, absolutely. So we definitely counsel patients before the genetic testing.

Dr. Rastogi:
Yeah.

Dr. Park:
So let's sum up what we discussed today.

Dr. Rastogi:
Right. Yep.

Dr. Park:
TKV is an important biomarker for assessing disease progression, and MRI and CT are both used to measure total kidney volume.

Dr. Rastogi:
And the Mayo Clinic Imaging Classification is an important tool to predict risk of rapid progression ADPKD patients in the five classes, prognostic in this classification, and patients who fall under classes 1C, 1D, and 1E are rapid progressors and should be considered for therapy with tolvaptan.

One of the other tools that is not used as frequently is the PROPKD score, and genetic testing as well. And these are complementary methods for assessing disease severity. Also, keep in mind that there are other factors too that will predict rapid progression as we discussed.

Dr. Park:
And definitely the total kidney volume should be used in tandem with the GFR to monitor renal function in patients with ADPKD, since, as we discussed, GFR can be preserved or within the normal range for a long period of time in early stages of disease, yet, patients may still have high risk of disease progression.

Dr. Rastogi:
Yeah. And last but not the least, we spoke about the imaging tests, the TKV, we spoke about the gene. But there are other factors too, that should be kept in mind. Male gender, they tend to be more rapid progressors, early hypertension, early urological complications, all these things can help predict which patients are more likely to progress more rapidly.

So with that, I think - I want to thank you, Dr. Park. This was - I hope the audience found this useful. Thank you very much.

Dr. Park:
Thank you so much for your time and attention today.

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