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Optimizing the Care and Quality of Life for Patients with ADPKD – Part 1: Detection and Diagnosis

Announcer:
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Dr. Chapman:
Good afternoon. I am Dr. Arlene Chapman and welcome to this webcast titled "*Optimizing the Care for Patients with ADPKD*". This is part one of four in our CME series on improving the care and quality of life for patients suffering from autosomal dominant polycystic kidney disease, or ADPKD. In this webcast, we are focusing on the detection and diagnosis of this disorder. I am Professor of Medicine and Chief of Nephrology at the University of Chicago and I'm joined today by my college and friend, Dr. Matt Lanktree of McMaster University. Dr. Lanktree, please introduce yourself.

Dr. Lanktree:
Hello, everyone. I'm excited to be here, today for this opportunity. Uh, my name is Matt Lanktree, I'm a nephrologist and geneticist at McMaster University in Hamilton, Canada.

Dr. Chapman:
Fantastic. So, let's review the learning objectives for this webcast. I hope that by the end of this module, you'll be able to recognize the pathophysiology and diagnosis of polycystic kidney disease, be able to describe the renal manifestations of ADPKD and the relationship to cyst burden or total kidney volume, kidney function, and genetic causes. We'll also review the extra-renal manifestations of polycystic kidney disease.

So, we'll start with a case, and this is a 40-year-old woman with polycystic kidney disease. She was diagnosed at age 27 as part of a family screening program. She occasionally had symptoms of early satiety and abdominal fullness. She has not described any kidney stones or nephrolithiasis, flank pain, hematuria, and she's otherwise been well. She's had one previous urinary tract infection, and two uneventful and full-term successful pregnancies. She currently takes no medications. She is a former smoker with 20 pack years, and she does drink alcohol. She is a teacher, and when she is seen in the clinic, her blood pressures are 147/80 mm Hg. Her heart rate is 92 and otherwise, her examination is normal and her kidneys are not palpable. She has two serum creatinine measurements documented, in 2008 and 2015, which were 0.8 mg/dL and 1.0 mg/dL. She's had multiple ultrasounds done with kidney lengths determined between 2007 and 2014, showing kidney lengths elevated on the right from 14.7 now to 16.7 and the left 14.0 now to 14.4.

So, in this module, some of the questions we're gonna be discussing will be what is the approach to diagnosis ADPKD? How does this form in ADPKD? What are the extra-renal manifestations of this disorder? What are some of the treatment modalities? And is there role for more testing in the management of these dis- these patients? Is it necessary? Does it change management?

So, for review, ADPKD is the fourth leading cause of renal failure. There's no race favored and it's a dominantly inherited disorder. There are more than three million individuals diagnosed worldwide and many more affected. The cysts are not limited to the kidneys and they're found in other organs of the body, including the liver, pancreas, spleen, and brain. And even though we typically see these patients in adulthood, it's important to remember that this disease begins in utero. Over thirteen million individuals are truly affected worldwide with differing prevalences in the United States, Europe, and Japan, having the lowest at 1.2 per 10,000 individuals.

There are now, in the United States, between 200 and 300 thousand diagnosed. This number qualifies ADPKD as an orphan disease. ADPKD results in 6% of all patients receiving renal replacement therapy and 10% of those under 65 years of age. The incident rates for ESRD are different between women and men being 6.1 and 7.5 per million population, respectively, indicating that women have a milder form of disease. Importantly, the incidence, the prevalence, and survival rates and age of onset of ESRD are increasing, suggesting positive impacts from therapy. And I'm gonna hand o- this over now, to my colleague Dr. Lanktree to help go through the issues related to heritability, diagnosis, and the role for genetic testing.

Dr. Lanktree:
Thanks, Dr. Chapman. So, ADPKD or autosomal dominant polycystic kidney disease is inherited in an autosomal dominant fashion meaning that you're required to have one mutation, on copy of the mutation inherited from your parents. Um, both men and women are equally affected, however up to 10% of patients have no identifiable family history. It's mutations in either PKD1 or PKD2 that account for the vast majority of patients with those with PKD1 having a generally more severe phenotype.

So, let's take a quick look at the diagnostic criteria for autosomal dominant polycystic kidney disease. It's important to remember that ADPKD is very different than just having a few simple cysts, and simple cysts are very common in the population. So, the ADPKD criteria which were first published by Ravine and subsequently revised by Dr. Pei and so it's often referred to as the Ravine/Pei criteria is based on ultrasound imaging in the context of a positive family history. So, since the number of cysts and total kidney volume increases over life, it's, it's age stratified. So, between the ages of 15 and 40, you're required to have a minimum of three cysts, between 40 and 60, you need a minimum of two cysts in each kidney, or four total cysts, and over the age of 60, you require more than four cysts in each kidney. Again, this is important that it's in the context of a family history because a family history increases the pre-test probability of having ADPKD to 50%. This is in contrast to a person with no family history in which case, their pre-test probability of having ADPKD is the population prevalence of the disease or one in a thousand. So, the test characteristics change significantly in that positive family history.

Repeat ultrasounds can be employed in patients with unclear histories because, uh, again, the number of cysts increase with age and the total kidney volume will also increase with age. Uh, additionally, so those extra-renal manifestations can also help to confirm the diagnosis. So, since liver cysts are so common, uh, their presence really can help add to the likelihood that indeed, it is ADPKD.

OK, so, after reviewing those criteria, let's return to the patient that we discussed earlier, that Dr. Chapman described. This was a 40-year-old woman who had a clear family history and was recognized to have multiple cysts on her kidney at age 27, which is part of family screening. Uh, again she does have some symptoms of an early satiety and abdominal pain but hasn't had any stones, flank pain, or hematuria. The, uh, ultrasound does show multiple various-sized cysts. So, it can be challenging sometimes if radiologists don't give specific, uh, numbers of cysts and their exact distributions. So, returning to the imaging, can really help with us to identify exactly the location and number. Uh, the size of the cysts, so while bigger and fewer cysts is common in people with PKD2 mutations, whereas th- those with PKD1 mutations are more likely to have a bag of marbles, many, many smaller sized cysts, the size of the cysts doesn't really help in the diagnosis. It's really just the number.

Additionally, you can see the enlargement. So, again, renal enlargement is pathognomonic for autosomal dominant polycystic kidney disease. So, even other less common conditions that have multiple cysts, um, they don't include the renal enlargement that's part of PKD. So, the trend of growing, uh, kidney size on these serial images is also in keeping with the diagnosis of ADPKD.

The role of genetic testing in PKD is most vital in the context of those without a clear, uh, diagnosis. So, especially in cases where there's no family history, where disease exclusion is required at a young age. for example, in the evaluation of a kidney donor. In the situation where there's large discordance in disease severity between family members or where there's discordance between kidney size and the rate of loss of kidney disease. If there's atypical imaging, so the kidneys are not equally affected, or if there's a consideration of a possible syndromic form of kidney cysts, uh, in a, in an unusual cystic kidney disease phenotype. So, you know, the diagnosis is generally, uh, ultrasound-based, especially with a positive family history. But genetics can be quite useful in, uh, confirming the diagnosis, especial- especially in these atypical cases.

There are significant challenges that are associated with genetic testing, however. Uh, cost, finding the provider, where to, uh, collect the sample and have it transferred, obtaining adequate genetic counselling and, uh, even interpreting the results of genetic tests can be quite challenging. And so, I really encourage people to consider referring atypical or unusual cases to centers of excellence where the diagnosis is a little bit uncertain.

Dr. Chapman, can you tell us a little bit more about, uh, how the cysts form and maybe some of the extra-renal manifestations?

Dr. Chapman:
Sure. I can, uh, I'd be happy to do so. And, um, I'm glad to hear how, uh, selective it is and needed for considering genetic testing in this

disorder. Um, and so I, I learned a lot from that.

You know, kidneys, uh, cysts are really the first verifiable primary manifestation of PKD. There really are no complications that can occur without the cysts being present. And it really is important to remember that all of our renal manifestations, whether it's hypertension, blood in the urine, kidney stones, kidney infections, reduced kidney function, almost always has an inverse correlation, uh, in terms of, uh, kidney cyst burden or kidney volume and, and their occurrence. So, the bigger the kidneys, the more often they happen. Uh, the bigger the kidneys, the lower the kidney function. And when, when it comes to the impact of cysts on kidney health, in general, there is a local infiltrating process of cyst expansion that results in recruitment of inflammatory cells, such as macrophages and monocytes and compression of surrounding healthy tissue. Um, and this becomes even more important when cysts are located deep within the kidney, where numbers of upstream nephrons and arcades of glomeruli can be really destroyed from one strategically placed cyst. So, it's not surprising that ADPKD, um, actually is a very focal disease, uh, only involving 5% of the nephrons, which is sufficient to actually replace almost all of the remaining non-cystic parenchyma.

These cysts develop as a focal lesion. They all have a germine mutation. But the process of a new cyst forming is most likely related to losing the second good copy of the PKD gene. And this is called loss of heterozygosity or second-hit. Once this occurs, each cyst behaves as its own, unique, genetic cyst pocket, almost recessive in nature at the tissue level, and it expands as a clonal set of cells, excreting fluid and expanding, uh, and ultimately de-differentiating time.

There are a number of different contributors to how this happens. And I know Dr. Lanktree has put together a very nice, um, uh, uh, algorithm for what leads to cyst formation related to, uh, polycystin deficiency. And perhaps he could share with us his views of the, um, pathways that are involved with this.

Dr. Lanktree:
Thanks, Dr. Chapman. Absolutely. So, it's the loss of that good copy of the polycystin gene, that loss of heterozygosity, that leads to a decrease in polycystin-1, polycystin-2 complex signaling, which leads to the rapid replication of those, uh, renal tubular endothelial cells that leads to the cyst formation. And then there's a subsequent snowball effect with inflammation, local ischemia, cytokine release, and tubular obstruction that all feeds back to further promote cyst generation and, you know, subsequent loss of kidney failure. As well as the issues within the kidney, itself, the loss of that polycystin signaling can also lead to extra-renal manifestations. So, things like intercranial aneurysms, which are found in about 5 to 10% of patients with polycystic kidney disease, uh, of which people are often screened for. Uh, additionally, you can end up with hernias and diverticulosis and of course, we can't forget the liver cysts. So, liver cysts, of course are the most frequent, uh, extra-renal manifestation of polycystic kidney disease and can even help us with diagnosis because they're so common, uh, typically in up- about 90% of patients with ADPKD.

Importantly, the kidney volume is really predictive of the complications of polycystic kidney disease. So, when people still have relatively small kidneys, uh, they're less likely to have hematuria and neurologic c- complications. They're less likely to have severe proteinuria, and it's only as the cysts grow larger and the total kidney volume increases that the likelihood of having these renal complications of kidney p- PKD increase.

So, um, can you maybe tell us a little bit more about some of the studies evaluating total kidney volume, Dr. Chapman?

Dr. Chapman:
Sure. Yeah. I'd be happy to. You know, um, it was really around, uh, the, the beginning of the millennium where, uh, there was a concentrated effort to determine a better way to track disease progression in polycystic kidney disease. Um, and many knew for a long time that even though kidney function was remaining completely normal, kidney size was growing, and cyst burden was increasing. And it was thought, not known for sure, that that growth was very, very important in predicting who was going to develop renal insufficiency and go on to renal failure.

So, the CRISP consortium was created, which stands for the Consortium for Radiological Imaging Studies of Polycystic Kidney Disease to choose, uh, s- a cohort of about 243 individuals with relatively intact kidney function who are relatively young, but yet had manifestations of, um, risk factors for, um, progressive renal insufficiency, meaning early onset hypertension before the age of 35 or detectable proteinuria, uh, which is relatively uncommon in ADPKD except for those individuals with, um, high risk for progression to renal failure. And these individuals were imaged using magnetic resi- resonance imaging for, um, three years in a row and it showed a dramatic, uh, amount of information that really was a paradigm shift for following patients with ADPKD. First, it showed that kidneys were growing exponentially, that that growth was almost entirely a result of cyst growth, uh, that resulted in, in the increasing kidney volume. And that there was a wide range of growth rate; some with relatively slow growth rates, but others with very malignant, very explosive increases in kidney size. And it turns out that on average these kidneys are growing about 80 mL per year, which is about half a kidney per year. And it was a year that this was finished and published that he number of therapies being tested in ADPKD suddenly jumped from one to twenty-two because now there was a way to actually measure disease progression.

The same thing that happened during, um, the duration of the CRISP study was that patients were monitored closely for the complications that patients with ADPKD can get. So, this includes following their blood pressure, determining if they developed hypertension, understanding the episodes of blood in the urine, following the urinary tract infections, and the nephrolithiasis, and not surprisingly, all of these increased with time over CRISP and they all associated with the size of the kidneys of the patients in this study. And it also associated with the rate that the kidneys were growing in size. So, for every 100 mL in total kidney volume, there was a 40% likelihood that someone would develop hypertension. For 100 mL increase in total kidney volume, there was a 20% chance of having pain or blood in the urine, and even furthermore, developing chronic renal insufficiency over time. So, using these measurements of kidney volume and in CRISP patients who'd had both ultrasound and MR imaging of their kidneys done, both were found to be highly sensitive for predicting who's gonna develop chronic kidney disease, to almost the same level of measurement. This isn't to say that we can use ultrasound to longitudinally follow kidney growth, precisely, but we can use ultrasound just the way we use MR to predict who's at high risk for progression.

So, these data have now helped us understand who the high risk individuals are, how well kidney function's compensated while kidney volume grows, and who we can tell in the future whether it's eight, ten, or fifteen years, who are gonna progress on to renal insufficiency or ESRD. If there's anything that we can do to change that growth rate, more than likely we're gonna delay their onset of renal insufficiency and ESRD. These are highly impactful findings from the CRISP study.

So, Dr. Lanktree, do you wanna take away our summary and key take-aways.

Dr. Lanktree:
OK.

Dr. Chapman:
From the diagnosis in kidney volume measurements for ADPKD?

Dr. Lanktree:
Certainly. Thanks, Dr. Chapman. So, it really makes you feel like a modern day fortune teller. I mean, using imaging, whether it's ultrasound or MRI, you're really able to gauge people's severity of polycystic kidney disease and the rate at which they're likely to progress towards kidney failure. I think you really showed some really excellent examples from the CRISP study and the association between kidney size and the kidney complications. And we also talked about the importance of genetics, especially in the cases, uh, that are a little bit more of a diagnostic dilemma in the situations where, you know, there isn't a family history or i- the, it doesn't all quite fit like our standard typical PKD patients. So, I, I hope that people are interested to move on to the additional modules of this course, where we're gonna go into more depth into risk stratification and potential therapies for ADPKD over and above the conservative approaches that are gonna be good for all of our patients.

Dr. Chapman:
So, I hope that what Dr. Lanktree and I covered today helped us reach the objectives of this session. Um, we talked a little bit about approaches to the diagnosis of polycystic kidney disease where imaging is the first approach in these individuals, usually using ultrasound, and cysts number and distribution based on the presence of a family history. Uh, we talked a little bit about the pathophysiology of cyst formation and that these are focal, clonal, out-pouchings usually set off by a somatic mutation or a second-hit in the PKD genes in the tubular epithelial cells, where they become a fluid-secreting pocket, uh, proliferating cells in a cyst-lying fashion. We briefly touched on the renal manifestations of polycystic kidney disease including hypertension, blood in the urine, nephrolithiasis, and urinary tract infections and their very tight relationship to total kidney volume.

The other relationship to total kidney volume that's very, very important is the relationship to kidney function, which is inverse, and proportionate to the increasing kidney size. And finally, the cases where genetic testing plays a significant role i- in ADPKD was reviewed in detail by Dr. Lanktree. In addition, because of the patient presenting with more than just disease in the kidney, we talked about the importance of screening for intracranial aneurysms in patients with a positive family history and the overwhelming presence of liver cystic disease, which is specific to ADPKD and how it can also manifest symptoms in patients with this disorder.

I think this is a nice way to transition now to the module two, where identifying those individuals at high risk for progression to renal failure will be discussed. Thank you so much.

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