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Released: 10/17/2022
Valid until: 10/17/2023
Time needed to complete: 30 minutes

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Imaging in the Diagnosis and Management of ADPKD

Announcer:
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Dr. Chebib:
Hello and welcome to this webcast titled, "Imaging in the Diagnosis and Management of ADPKD." I'm Fouad Chebib, a nephrologist and Assistant Professor of Medicine at Mayo Clinic, Florida, and I'm joined today by my colleague, Dr. Theodora Potretzke, so please introduce yourself.

Dr. Potretzke:
Thanks so much, Dr. Chebib. I'm really happy to be here with you to present this webcast today. I'm Theodora Potretzke. I'm an Assistant Professor of Radiology at the Mayo Clinic in Rochester, working in abdominal imaging.

Dr. Chebib:
Before we get started, let's review our learning objectives.

Dr. Potretzke:
Thanks, Dr. Chebib. So, if you're a radiologist, you will find some really helpful updates and pearls which are really going to allow you to become a strong and valuable link in the chain of ADPKD care. More than ever, quality imaging and quality image interpretation is really essential, as Dr. Chebib knows, for the appropriate evaluation management of these patients. These are our objectives. By the end of this seminar, we expect that you will be able to describe the role of imaging in the diagnosis of ADPKD, but that's not all. We want you to also recognize the typical versus atypical presentations on imaging of ADPKD. By the end, you'll be able to summarize the importance of total kidney volume as a prognostic biomarker, and also be able to compare methods for assessing and determining this biomarker of total kidney volume.

So, to start out, we're going to take a bird's eye view of the overall diagnosis and treatment algorithm for ADPKD that Dr. Chebib and Dr. Torres published initially back in 2018. You know, I really love this algorithm, Dr. Chebib. So I'm going to show this to you all now, to introduce you to the elements of care that do utilize imaging, because it's not just one. We're going to talk more about each of these steps in this seminar. So, recognizing renal cysts, confirming a diagnosis of ADPKD, those are our first steps that we're going to discuss, again determining whether the pattern is typical or atypical, which as you can see, is the first branch point in this algorithm that the nephrologist is going to be using, and in a case of a typical pattern of ADPKD, which is really the majority of the patients, we're going to talk about the really important issue of total kidney volume. When I think about the role of imaging in the diagnosis of ADPKD, I try to put myself in your shoes, Dr. Chebib, and think about the patients that you're seeing. When you're trying to make a diagnosis of ADPKD, it's not just one-size-fits-all. The three diagnostic scenarios that, you know, I've seen that you encounter in your practice, are the following. So you have the patients who have a positive family history, that you're seeing, really for screening. And in those patients, ultrasound seems – especially in young patients or patients with a, you know, a small body habitus or no symptoms – ultrasound can be a great

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technique and a great modality to use. But then again, you have patients that have a different presentation. You can have those with symptoms, whether they have a family history or not. Patients who come with hypertension, hematuria, proteinuria, renal functional decline, flank pain maybe due to cyst hemorrhage, or even stone disease. Now, for any of those reasons, they might be coming to a nephrology clinic, and if there's a positive family history plus symptoms, well, ultrasound may be an acceptable modality. Sometimes in these cases, you may choose CT or MRI. Is that correct?

Dr. Chebib:
Yeah, absolutely. So with ultrasound, that's a great method for screening, but then after the diagnosis is made, whether for symptoms or incidental, then we would like to get the CT scan or MRI, to improve our prognosis, to kind of really look at the pattern of the cystic burden, and then compare that to the renal function at the time. As you kind of mentioned, and in the next few minutes as well, how it's very important to look at these patterns, and try to discern, kind of, that – confirm the diagnosis and then obtain a good prognostication through the CT scans and MRIs. So, hopefully, that will be clear also in our message here.

Dr. Potretzke:
Absolutely. I agree 100%, and thanks for reiterating that. You know, each of these modalities may have a role, and an important role. The other thing we as radiologists sometimes see is that absolutely incidental diagnosis of ADPKD, in an unsuspected case when's someone getting imaging for a totally different reason, of the abdomen and pelvis. We have occasionally seen incidental diagnoses of ADPKD, so that can come with any of these modalities.

So let's move forward and talk about the diagnostic criteria on imaging. What I want to reiterate here is that confirmation of ADPKD is primarily by imaging. We think a lot about genetic testing, and it's very important in the clinic, but we can confirm a diagnosis of ADPKD by imaging, in most cases. One thing that's an important take-home message here is that the criteria for ADPKD by imaging differs, between - for patients who do have a family history versus those who do not have a family history of the disease. So we're thinking about a positive family history, and we're looking at bilateral cysts. The criteria for number of cysts to make the diagnosis is fewer in a younger patient, so for those less than 40 years old, three cysts bilaterally, in the 40-60 year old age group, four cysts bilaterally, typically two in each kidney, and then for those who are greater than 60 years old, eight cysts bilaterally needed, to make the diagnosis, even in those with a positive family history. Now this is because, you know, benign renal cysts do increase with age. They become more common in the older age group, not related to a hereditary disorder. So the diagnostic criteria for ADPKD in an older patient is a little bit stricter.

Now, let's talk about those without a family history of ADPKD. With no known family history, a larger number of cysts is needed to make the diagnosis. We need to see 20 cysts bilaterally, in total, and also need to show some other element of the ADPKD phenotype, the most common that we would see on imaging being liver cysts, and the more you look at these patients, the more you notice that liver cysts are very common in ADPKD patients. But if you have a patient with no family history, who has at least 20 cysts, you know, shown bilaterally – in both kidneys, 20 cysts total – and also has liver cysts, that can be sufficient to make a diagnosis on imaging.

So now that we've looked at what the criteria are, let's talk about how well they may perform. So, the cyst criteria have been studied extensively, and when they are used to make a diagnosis in someone with a positive family history, they have 100% positive predictive value for the numbers that I reviewed. So look at this table here, by age group. In the youngest age group, of course three or more cysts. In that middle, 40-59 age group, two on each side or four total – 100% positive predictive value. And also in the older age group, eight total or four on each kidney, 100% positive predictive value. So this is really, really helpful data to know how well this performs for making a diagnosis. We also use this cyst criteria for excluding a diagnosis of ADPKD in those with a fom – positive family history, which as you can imagine, is really important to the patients you're seeing in clinic, if we can exclude the disease. So, here those criteria are listed, along with their negative predictive value, the best negative predictive value, of course, being in those older age groups if you've gotten to above 40 years old with two or fewer cysts, we exclude the diagnosis of ADPKD, again with great data to support those thresholds.

So that's a review of the diagnostic criteria we used in the population, maybe for screening with a family history, which is helpful, but I do want to make the point, looking at a case here, which is a non-contrast CT showing both the axial and coronal images through the kidneys, that counting cysts is not always necessary. You will not be counting cysts in a case like this. And again, we want to be practical and clinically-focused in our practice and in this seminar. Here's a case of markedly enlarged kidneys bilaterally, with cysts that replace the parenchyma, involving upper and lower poles diffusely, and we see liver cysts as well. This is a clear case of ADPKD, if in the clinic, the clinical assessment matches this imaging diagnosis and they are concordant. Here the imaging findings would certainly support a diagnosis of ADPKD, with certainly greater than 20 cysts in both kidneys, renal enlargement and liver cysts. These are the things we look for, and this is a common appearance of the patients that you see in your clinic, Dr. Chebib.

Dr. Chebib:

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Yeah, absolutely. We see, in our PKD clinic, so many times even without the family history, this is very diagnostic. There is not a lot of other diagnoses or entities that can cause bilateral enlargement, bilateral number of kidney of cysts, so many cysts, hundreds of cysts. There are a very few rare things that could mimic that, so that comes kind of with a – if there's other external manifestations, like cleft palate or extra digit, or something unusual, then, you know, putting those pieces of the puzzle together would incline us to get more genetic testing, as well. But for the 99% of the time, there is nothing on there, then ADPKD that can cause this __.

Dr. Potretzke:
So looking back at our algorithm, we have identified renal cysts, we've learned how to confirm a diagnosis of ADPKD, and the role of imaging in that step. Now let's look at this fork in the road, where we have to decide is it a typical pattern or an atypical pattern? The typical pattern of ADPKD is just like the case I just showed. 95% of cases will follow the typical pattern of ADPKD, where we see bilateral and diffuse distribution of cysts. There can be mild, moderate or severe replacement of the parenchyma. Another way to say this is that all cysts contribute equally to the increase in size of the kidneys which we see here.

So what is an atypical presentation? Well, it has its multiple subtypes, really six clear subtypes, and while it is much less common than the typical presentation, these atypical manifestations of ADPKD are truly important to recognize, because they will be triaged and managed differently in clinic. So the manifestations we see here, which are atypical, may be a markedly unilateral distribution of cysts, cyst distribution, which is segmental, perhaps involving the upper pole, like here, bilateral cysts but with a very asymmetric distribution, a lopsided pattern where you have really big cysts contributing to volume increases that are, you know, variable in their placement.

A case of ADPKD here which shows unilateral atrophy, which of course is atypical, and then a case where the parenchyma is atrophied bilaterally. All of these would be considered an atypical pattern of ADPKD, and would warrant a different type of management approach, So again, important to recognize the difference, and I'll show a case here, of a coronal image from an MRI, through the kidneys of a patient with ADPKD, and you can test yourself here to decide is this typical or atypical? I think we can agree that we see bilateral renal enlargement, which is symmetric, with a diffuse distribution of cysts involving all segments of both kidneys, and therefore, this fits into the typical pattern of ADPKD.

So that's all there is to looking at that typical versus atypical pattern. Again, we all need reminders sometimes on what the atypical patterns might be, but just important to recognize when a case doesn't fit into that bilateral, diffuse cyst distribution. But for those that do, I want to get into the discussion which is really at the heart of this collaboration and this webcast, which is kidney size and its importance in predicting renal functional decline. Dr. Chebib, can you talk briefly about how that's changed the clinical approach to ADPKD, knowing what TKD can really predict?

Dr. Chebib:
Yeah, so TKD has been really instrumental in pushing the field really forward, and we don't say that lightly. So of course kidney volume has been FDA-approved as prognostic biomarker after long studies looking at the natural history of causes of kidney disease. So after seminal and landmark studies, looking at the natural history – so that's CRISP – the CRISP data, eventually we – and with other studies, we realize that total kidney volume, so how big both kidneys are, would give us a great idea of who has more CD or disease than other, and that kind of propelled, kind of, the understanding who would be eligible for clinical trials, and then how to move forward also in prescribing disease-modifying treatments. So really, it's kind of at the center right now of our clinical practice, and hopefully in the future, there will be also additional advancement in imaging biomarkers, but at the moment, this is the standard of care is to get – to obtain appropriate kidney volume and classify the patient into typical __.

Dr. Potretzke:
That's such a helpful overview of why this is so important, and when I, you know, became involved in this practice and with you and your colleagues, really coming to appreciate that this disease does have a variable phenotype was extremely important. And I'm glad you mentioned the CRISP study. We do have a slide here which I wanted to show, which shows some of the data from that, which looked really closely at patients with ADPKD who are at risk of progressing to end-stage renal disease or chronic kidney disease with kidney failure, and looked at their cyst volume, and I love that this shows that there is some heterogeneity.

So with kidney volume on the Y axis, and age on the X axis, we can see for any given patient, there's a pretty predictable course but each patient is quite different from the other. So we have some patients, toward the left side, which at a young age may show a high kidney volume and increase rapidly, whereas we have some patients who in older age, still have a fairly low kidney volume relative to others with the disease, and progress more slowly. And I would imagine that when you're seeing your patients in clinic, one of their main questions is if and when they will need dialysis or kidney transplantation. And I imagine that this is really what helps inform you of that.

Dr. Chebib:
Yeah, absolutely, and then so in addition to just taking a total kidney volume, which is a number, and that – you have to – so it's important as a clinician to correlate the number with the clinical presentation. So – meaning that age at the time of the total kidney

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volume, the kidney function as well, so there's additionally something called the __ classification that you will be sharing with us shortly. But that's a gauge-adjusted total kidney volume that helps putting into context that total kidney volume at time of imaging. And I would really, as a predictive tool on trying to understand the future, GFR and then that would give is – that gives us a tool on understanding when the patients get each kidney failure, and that's really the most important information I could ever share with a patient with autosomal dominant polycystic kidney disease, because they – we owe it to them to predict, kind of what their disease is going to look like, and then how they are going to prepare their life around the time of kidney failure, to be able to get either preemptive kidney transplantation or prepare accordingly before renal replacement therapies.

Dr. Potretzke:
Exactly, and we'll get to the classification system definitely. Thanks for mentioning that. I do want to show this slide, again showing that on imaging follow-up, looking at total kidney volume is extremely important because renal function itself, which Dr. Chebib mentioned already, at a certain timepoint, especially when a patient is young, cannot predict future decline. Kidney volume can. So larger kidneys at an earlier age will be predictive of future EGFR decline, and sort of help you and your patient understand the trajectory that they're on, looking at the CRISP data and how they may match up with that. So here's an example again, of two patients and I like to say that not all ADPKD patients are alike. These are two patients with typical pattern of ADPKD, with very different total kidney volumes. I showed this – this is the output that we use at our own institution when we measure ADPKD from MRI. I'll explain that a little more toward the end of this talk, but here we have, again, both patients with typical ADPKD. The total volume in one of these patients is 1,359 cc, whereas in the other patient it is 7,956 cc. And that's a very different conversation that you'll be having in clinic with these patients.

So, to get back to the classification, here's a display of the Mayo Clinic TKV classification, based on the data we've been referencing. The patients, as we saw, that have a lower volume and progress more slowly are down as Class 1A or Class 1B – slower growth. Certainly their kidneys continue to grow every year, and continue to be followed, but that growth is slower, whereas the Class 1C, 1D and 1E patients, who may start out with a larger volume earlier in life, also have a rapid – a more rapid growth rate with the Class 1E being the most rapidly progressing. But Dr. Chebib, we talk about the term "rapid progressors" or patients at highest risk for getting to chronic kidney failure. Is it Class 1C, 1D and 1E patients who will be in that category?

Dr. Chebib:
Yeah, so as you mentioned, there is a risk and there is evidence of rapid progression, and this is kind of to differentiate two, kind of groups of patients – the ones that are going to reach kidney failure early on, and kind of we created the definition that by age 62, which is the 75th percentile of the population with ADPKD. So these patients are who are at risk of rapid progression. They are under the Mayo Class 1C, 1D, 1E. And then, 1A and 1B are considered slow progressors. Some groups consider 1B as intermediate progression, but for the most part, we are quite aggressive in trying to slow down the disease trajectory for the Mayo Class 1C through 1E.

Dr. Potretzke:
So I want to reiterate for our listeners that total kidney volume, not only informs the conversation about disease prognosis that you have with your patients, but it could make these patients eligible for a disease-modifying therapy that is FDA-approved. So, that's really where the importance of this biomarker lies.

Let's talk a little bit more about imaging modalities again, when we're talking about TKV. I'm showing some images here of ultrasound. We know ultrasound has a great role in looking at the kidneys and in renal cysts, but this is really up to a point. When we are trying to define total kidney volume in patients, especially those who have large kidneys and are at risk of rapid progression, ultrasound does fall short. So we can see in this example here, that estimating the length of the kidney is really problematic when the kidney can't be imaged in a view in sagittal, on ultrasound here. We calipers that are falling outside the visible kidney and we're not catching the lower or upper poles. So I think the ultrasound, while it has a great role for screening, and in smaller kidneys, and in the asymptomatic patients with a positive family history, it has a limited role when we're talking about TKV. CT and MRI are where we go for our kidney volume calculation. We use MRI here, but it can also be calculated by CT. So the methods that have been used for assessing TKV, I sort of think of as the practical methods that can be used in your clinical practice, and those that really lay the foundation for this research work and our knowledge in our clinical trials, which are a little bit more arduous.

So, in clinical practice, we're going to review the ellipsoid methods in clinical practice – total precision is a little bit less important. Clinical prognostication can be made with results from an ellipsoid calculation, which are very easy to do manually on CT or MR images. In clinical trials, in the gold standard techniques are manual planimetry and stereology, which do require either a lot of manual work or special software to calculate TKV, but have been really important, as I said, in understanding the importance of TKV in this disease.

I think where we're going, with methods for calculating TKV before we get into the ellipsoid equation itself, where we're going is potentially into automated or semi-automated methods of measurement. For those who are exploring machine learning applications in their radiology practice, this is a great area to look into. Organ segmentation is a great application of machine learning, and we use it

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now in our practice, implemented in the clinical work flow for segmentation of the kidneys in ADPKD patients, showing excellent performance compared to reference standards. Our protocol here is a simple non-contrast, abdominal protocol on a 1.5 Tesla scanner, and from our coronal SSFAC sequence we apply a machine learning algorithm to calculate total kidney volume via this organ segmentation. But to look again at the ellipsoid formula, which is widely used and reliable for prognostication of TKV calculation, here you would take 3 perpendicular measurements of the kidney, to approximate the TKV. We use ellipsoid formulas elsewhere in radiology. Again, it's a volume transfers by AP times cranial/caudal times pi over 6, which is 0.52. And that gives a good estimate for the total kidney volume. Here you can see it applied in 2 different cases. If you decide to use that type of process, which again is really accessible, the Mayo Clinic PKD Center does offer a website here, to plug in those measurements to calculate the TKV itself, just as we saw in the last slide. Give your total kidney volume, and then even determine the Mayo Clinic calcificat – classification, excuse me, using the TKV and the patient height and patient age. So, it's accessible here to go in and use that website. We use coronal and sagittal, averaging those, and then of course, the AP and transverse dimensions, and you can follow step-by-step there. And even use our data estimate the future EGFR and time to end-stage kidney disease there, on that website.

So I think, Fouad, you've used this in your practice, probably before we were doing our automated segmentations, and tell us how you found doing the ellipsoid calculations, or any tips you have for those out there listening.

Dr. Chebib:
Yeah, so I still use both, kind of the automated methods which have been a great advance in our practice. But I also sometimes, if the patient is bringing their own CT scan or MRI, and it's uploaded in our system, I would go in and kind of review the images, first to kind of see the cystic burden and make sure they have the right diagnosis.

Then I would measure, as you mentioned, all the different dimensions and calculate them on the online calculator, and then with that, I would get the right kidney, left kidney and the total kidney volume, and get them the imaging classification. So, initially, it used to take me 5-6 minutes, now it takes me 1-2 minutes, so I know time is very valuable in all clinical practices, whether from radiology or nephrology, but we owe it to the patients to let them know how severe their disease is, and how do we predict their future GFR and the onset of kidney failure. So I think that's really the most important information you – at least in one of the visits, needs to be done. It doesn't have to be repeated every six months or a year, maybe every 2-3 years we could repeat a CT scan or MRI to review the total kidney volume. But really the take-home message is if you have a fancy machine learning, AI algorithms, it makes our lives very easy, but it doesn't have to be that way. You can, whether as a radiologist, you can offer that to your nephrology group by measuring these. It probably takes you just 30 seconds to do these measurements, and then report the total kidney volume in the report. Then as a nephrologist, if you just see the images or you don't have that type of support from radiology, you can still do that in your clinic as long as you're able to scroll through the images and then do some measurement that would give you, in millimeters or centimeters, the dimensions. That's relatively simple, and it's a practical tool, and I hope we kind of showed the importance, and the practicality of that as well.

Dr. Potretzke:
I agree, 100%. I think it's something that radiologists can definitely tackle. We do things like this all the time, so integrating it into your dictation template, or your workflow, is really valuable and helps promote this collaborative type of relationship. So some important takeaway points I think, are that, you know, imaging plays a key role in confirming the ADPKD diagnosis. Diagnostic criteria do differ for those with and without a family history. TKV is an essential prognostic biomarker, not just valuable but really essential now, because it predicts future loss of kidney function, and identifies high-risk patients, also called rapid progressors, who may benefit from novel disease-modifying therapies. TKV can also identify those for whom reassurance and monitoring are appropriate, which would be really helpful for a patient and their family to know. And really a strong radiologist and nephrologist relationships is crucial for providing the necessary information that can aid in providing best care for patients.

Dr. Chebib, I want to thank you for inviting me to collaborate on this webcast. I really hope that our audience out there has learned a little bit about how important these considerations are in imaging of ADPKD patients. Thanks, everyone, for tuning in.

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