PEDIAPOD JANUARY 2021 TRANSCRIPT

Geoff Marsh
Hello and welcome back to Pediapod's first episode of 2021. It's good to have you back. This month we explore the impact of pediatric chronic kidney disease on the brain.
Pediatric chronic kidney disease results in a lifelong burden that requires routine care. Neurocognitive dysfunction, specifically impairment on tasks of executive function, is a well established comorbidity, but there is a paucity of data exploring the neurobiology of these cognitive deficits.
In this episode, I speak to this month's highlighted early career investigator, Dr. Lindsay Harshman, a pediatric nephrologist at the University of Iowa Stead Family Children's Hospital. She and her team used structural magnetic resonance imaging to compare the brain morphometry between early stage pediatric chronic kidney disease children and their typically developing peers, as well as linking this brain morphometry with disease status and performance on neurocognitive assessments.

Dr Lyndsay Harshman
Pediatric nephrology may not be everybody's first choice on their list when they go into medical school or pediatric training. I had an excellent inpatient rotation and saw some extremely complex kids, and seeing the ability of the nephrologist to actually have a direct and meaningful impact, and to be able to integrate physiology, immunology, pharmacology, all of the 'ologies', into the care of these patients was just tremendous. That really impressed upon me that, yeah, this is what I want to do. I can have an impact in this field.

Geoff Marsh
And so where do you stand between clinical work and research.

Dr Lyndsay Harshman
So currently, I'm on the end of a five year K award from the National Institutes of Health and an early career mentored research grant. So coming out of year five here and working on getting my own kind of 'big girl' grant, I guess you could say, after I've transitioned out of this one. So technically 75% of my time is research, which is phenomenal. I'm really well protected in that regard. And then the remainder is clinical.

Geoff Marsh
A primary focus of your research, which you've spent so much time on is pediatric chronic kidney disease. I don't think we've actually discussed that on Pediapod before, so I wonder if you could give us a really short summary of what it is, its prevalence and its pathology?

Dr Lyndsay Harshman
The primary cause of pediatric chronic kidney disease is congenital anomalies. So kids are born with something that lends to kidney dysfunction. We often think of it as a piping or a plumbing issue, that the kidneys don't drain well into the bladder or the kidneys are not formed well. That's the majority of cases

of chronic kidney disease. There's been really nice data published from the Chronic Kidney Disease in Childhood cohort. A component of the study, the ‘CKiD’ study, looks at cognition. It does continue to support that our patients, overall, do fairly well in school, maybe slightly below average on certain academic domains, but if you look at the kids overall compared to their peers, they do have executive function issues. So rather than having a global cognitive deficit, they have more of these subtle deficits that in the long run actually can really add up to be pervasive in work-life balance.

Geoff Marsh
But that's not to say that we have quite caught up with the neurobiology of how the brain is perhaps interfacing with the kidney...

Dr Lyndsay Harshman
You know, on the pediatric side, there really has been a paucity of studies looking at this and the studies that have been done are looking at a very general sample. But I do think that one of the big strengths of the data we have from my lab is that we have kids in a very well defined cohort, all congenital kidney disease patients, and we actually have real-time lab data that goes along with their visits so it's very well characterized.

Geoff Marsh
Were there differences then in the morphometry between your control group and your pediatric CKD children?

Dr Lyndsay Harshman
Yes, there were definitely morphometric brain differences between the two groups, where we see that the cerebellum volume is definitely smaller in the chronic kidney disease patients and that the cortex volume is actually substantially bigger. One thing that we had been mulling around, and that I think is a very reasonable hypothesis, is that particularly the gray matter in the cerebral cortex, it has a very delicate pruning cycle when patients are growing and developing, and it seems like the cortex, the gray matter within our pediatric CKD patients, is definitely abnormal and potentially subject to a pruning defect. Certainly one could ask- is having a chronic kidney disease process itself potentially driven by underlying genetic variants and does that same process actually change how the brain grows? I think that's a question we have to continue to ask. Are subtle genomic variants draining both ends of this? But in our paper we were definitely able to plot out quite nicely that lower estimated glomerular filtration rate is associated with lower brain volume within the cerebellum and so that certainly supports the idea that there is a disease-driven component of this potentially, in addition to other factors that we just don't understand yet.

Geoff Marsh
As you said, in parallel to these imaging studies, you were doing cognitive assessments as well. Did those results mirror previous findings?

Dr Lyndsay Harshman
Yes, that was actually really gratifying to see our data do very nicely replicate what's been done previously. Data from the CKiD cohort, which has a robust patient volume has really nicely shown that

IQ/ intelligence is overall fairly stable for our pediatric CKD patients, maybe slightly lower compared to healthy controls, and that's what we showed as well. In our data, compared to other data sets that are out there, we do see that there are very subtle executive function deficits, and then behavior control, as far as executive function goes, impulsivity, certainly we see it as a more of an issue in our cohort and that's very clearly replicated with other studies that are out there as well.

Geoff Marsh
I suppose you'd be more confident saying that the structural differences in the brain could be responsible for some of those cognitive impairments. What might be slightly more up for debate is how exactly renal function is affecting the shape of the brain or vice versa. What's your thinking on the mechanism and the direction of causality here between renal function and brain morphology?

Dr Lyndsay Harshman
I do think that the directionality between renal function and brain morphology is circular to some extent, to be very honest about it. I think that lower kidney function does probably drive what we see on brain morphology, but yet, I do think that in that kidney disease abnormality to the brain, there is sort of a circumferential redirection, whereby the underlying drivers of kidney disease may actually have a neurobiological impact on the brain. So there are some of those studies that we would just have to potentially in the future take back to even mouse models and look at how different genomic variants or knockouts in mice could predict what we see on the brain as well.

Geoff Marsh
Yeah, because you said that the majority of pediatric CKD patients did have a congenital disease. Have you got plans to go searching for genetic variants which are associated with it?

Dr Lyndsay Harshman
There is some nice data from Ali Gharavi's lab at Columbia University that looks at the Association of genomic variants on cognition. That data was actually fairly closely aligned with the CKiD cohort which has a wealth of data available to look at and to do association studies. So with the genomic variants that the Gharavi Lab looked at, they do see that certain genomic variants, oftentimes single nucleotide polymorphisms, actually do play a role in cognition- things like executive function and even one's state of anxiety. So I think it's a very reasonable next step to say, how do we use data that's already available, some of our knowledge to these genomic variants that are out there, look at them within my cohort, other cohorts. And again, recognizing you need to go to other centers and work together to be able to get a critical mass to really fully disentangle these questions. Some of the new data that we have coming out of my lab has actually looked at markers of brain injury- things like a protein called neurofilament light chain. It's a marker of axonal injury or white matter injury. I've really just been going through these biomarker samples recently and seeing that the kids that have longer duration of chronic kidney disease have higher levels of these white matter injury biomarkers and that does definitely associate with what we see on some of our brain imaging in my lab. So that certainly lends to an idea that yes, there is a longitudinal component to this. We need to have a larger sample, we need to be able to work with other groups and really get data in congregate.

Geoff Marsh

In terms of searching for therapeutic targets, is that something that you're looking at? And which way would you go? Would you be focusing on the kidney or the brain?

Dr Lyndsay Harshman
Yeah, that's a great question. Therapeutic targets I think are always on the mind of a clinician-researcher. What I would anticipate we look at are markers of chronic kidney disease control. Are we needing to do a better job with high blood pressure or hypertension control? There's other data that's out there that I've published as well looking at the effect of acidosis or low bicarbonate on the brain and this has also been published in the adult world as well through the chronic renal insufficiency cohort, looking at the effect of acidosis on the brain. It definitely seems like having better control of the metabolic acidosis component of chronic kidney disease probably has an impact on the brain as well. I don't think we fully understand it yet but it's fair to say that better control of acid-base balance in our patients, and then better control of hypertension probably are two of the quote unquote ‘easiest’ things we can do, and also the most practical things we can do as pediatric nephrologist, to potentially diminish the impact of disease on the brain.

Geoff Marsh
That was Dr. Lindsay Harshman, a pediatric nephrologist at the University of Iowa Stead Family Children's Hospital. That's it for this episode. As always, we'll be back next month and I hope you'll join us again then. I'm Geoff Marsh. Thanks for listening.