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Dr. Steph Dewar: From UPMC Children's Hospital of Pittsburgh, welcome to That's Pediatrics. I'm Steph Dewar, one of the hospitalists physicians here at Children's, and co-director of the Pediatric Residency Training Program.

Dr. J Williams: And I'm John Williams, chief of Pediatric Infectious Diseases. And, we are delighted to welcome as our guest today, Dr. Cassie Torok, a pediatric rheumatologist and a specialist in pediatric scleroderma. Cassie, welcome to That's Pediatrics.

Dr. C Torok: Thanks, John and Stephanie.

Dr. Steph Dewar: So, Cassie, you have a wide range of clinical and research interests. The one thing I thought would be useful for folks to hear about is your work with patients with scleroderma.

Dr. C Torok: Okay, great. So, I'll give you a little bit of background. I was a trainee here, and during my training and part of my fellowship training, I worked with Dr. Thomas Medsger, who's a world-renowned scleroderma expert in the adult world. I followed him and performed research and, in that methodology, really got in tune with scleroderma and then branched this into pediatric scleroderma, both localized scleroderma and systemic scleroderma. With that, we started a pediatric scleroderma clinic in 2012ish, and over time it's expanded. So, clinically, I'll see these patients on a day-to-day basis. We have weekly scleroderma clinics right now.

From that, I saw some issues that need to be addressed. Some are clinical issues as far as day-to-day management and treatment of these patients and then, also, education. Some patients would come in from different providers being misdiagnosed or managed in a different way. Then, also, the biology behind the disease is very unknown. It's not a disease that's tapped into as much as far as the research realm. So, I was very interested to find out what's driving this disease and how can we treat it, and how can we treat it better? So, as part of this scleroderma clinic, we also collect blood specimens on these patients and follow them longitudinally. Hopefully, then to find biomarkers and other indicators of what's driving this disease and how we can stop it and also, hopefully, maybe someday, find a cure.

Dr. J Williams: So, Cassie, you're the director of the Pediatric Scleroderma Clinic and this is a pretty uncommon disease and, therefore, you have kids coming from short of all over to see you as an expert. Correct?

Dr. C Torok: Correct. So, this an uncommon condition, so a pediatric rheumatologist, in general, is not that common to find. But, even an established pediatric rheumatologist may only see a handful of these patients a year. Maybe one or two patients. Therefore, if a patient has more severe disease, like linear down their leg, they're getting joint contractors, some limb length discrepancy, they would tend to reach out to me, maybe just to discuss management. But, a lot of the time, the parents would also be appreciative of a visit with me. So, they will fly out and see me even if it's just a one-time visit, and then I help co-manage with their pediatric rheumatologist. But, several of the patients after coming to the Pediatric Scleroderma Clinic actually like to come at least on an annual basis just to have a check in with me and then I'll report back to their primary pediatric rheumatologist or dermatologist.

Dr. Steph Dewar: So, Cassie, you mentioned that you did your training here and how you became interested in scleroderma. I'm just wondering, was there something particular about that disease process or rheumatology, in general, that sort of got you going down this path?

Dr. C Torok: Yeah. So, on a personal note, back in high school I actually was on Minocycline for acne, and this was before this was a known entity, but I had drug-induced lupus. Had arthritis, the typical morning stiffness, swelling, et cetera, some pericarditis, things of that nature. And, was seen by an adult rheumatologist and actually, I remember my experience with an adult rheumatologist as a teenager. This was back before pediatric rheumatologists were a little more common. I then went to medical school at Hersey and ran into Barb Ostrov, and she's still one of my mentors, and asked her, "Hey. Can I do an elective in pediatric rheumatology?" She opened me up to the rotation. The first day, I fell in love with it. I saw people with periodic fever syndrome, Raynaud's, pernio, dermatomyositis, things I've never heard of, as a medical student, and knew that that was for me. It was actually during my time with her where she was presenting a case of atypical lupus that I kind of diagnosed myself, along with her, that I had Minocycline-induced Lupus, in retrospect. So, that's how I got interested in pediatric rheumatology and actually fast-tracked while I was here and just did two years of general peds and then applied and went into the fellowship right away.

Dr. J Williams: God, it's so fascinating how one's experience leads you to a field where, as you mentioned, there are not a lot of pediatric rheumatologists, so the need is great. But you didn't come to the field necessarily just because of the need there, but because of your own experience. So, that's how you got clinically interested in these diseases and taking care of these kids. How did you become interested in doing the kinds of research you do on these diseases, which include really basic laboratory techniques?

Dr. C Torok: Yeah. So, the research component came from wanting to understand some of the biology behind it. We would see kids with very active disease. Typical treatment is steroids or methotrexate and some would respond, a fair amount do. But then, some would break through and keep having ongoing disease

which would cause further decrease in the size of the leg, or joint contractors, et cetera. Trying to understand the biology, maybe other medicines that are already available may work for these patients. That's why I work for biomarkers, looking at biomarkers in the blood and in the skin during active disease versus inactive disease, seeing if maybe a TNF-alpha, or something like that, is elevated in active disease. Then, we could use drugs that are already available such as Enbrel or Humira for this condition. We just haven't tried those yet, just because those are kind of more standard for the juvenile arthritis. So, finding some biology behind it to understand what drugs that are available now that might be better treatments, but then also, opening the door for further research into maybe newer molecules that haven't been identified that could potentially be developed to treat this better.

Dr. Steph Dewar: So, you mentioned that some of the patients that come to you have been misdiagnosed, or perhaps not treated. I'm just curious, are there common themes behind the misdiagnoses?

Dr. C Torok: That's a great question. When I give some education conferences this is usually what I talk about, how they present. Because it's important for the general pediatrician providers to understand different ways it can show up. I've actually had kids come from hematology clinic because they had this bruise that wouldn't go away. Typically, a localized scleroderma, or also known as morphea lesion, will start as, sometimes, an erythematous or violaceous linear band and it may look like a bruise in the beginning. But, if it's a bruise and it's still there after six months, and then it starts to get a little hard or turn a little brown, usually that is starting to change into the linear scleroderma or morphea. So, yes, it's the bruise that won't go away. I've had, also, kids have a smaller hand, finger, the leg. They might go to neurology or genetics to try to figure out why is the limb slightly smaller? But, unless you're actually feeling the skin or deep into the fascia, you wouldn't realize that maybe they have deeper skin fascial or muscle involvement from the linear scleroderma.

I've also had kids come with joint contractors because it goes from the skin down into the tendons and ligaments. So, this is an inflammatory disease, it's also fibrotic. So, the inflammation then leads to fibrosis or increase of collagen deposition in the tendons, the fascia, et cetera. So, they might come to me with a joint contractor. So, they may come from hand surgery because they have this finger contractor, they can't open their fingers and they were told it was from texting. But, if you actually feel all the way up the arm it may be some more indurated areas up in the fascia of the forearm that's giving a pulley effect, pulling down the fingers.

The other area to be knowledgeable is about new seizure in a child, just to kind of screen and look for skin findings. The patients with linear scleroderma of the head, about 20% can have some CNS or neurological issues. Sometimes, it's a white matter lesion in the line of the area, sometimes it's uveitis or eye changes, papilledema, et cetera. And then, there have been kids that have actually have presented with seizures and then later, it was noticed, "Oh, they have a faint

erythematous linear band on their face." We've had a few patients that I've shared with neurology that have presented that way. And, we're actually working getting a publication to a pediatrics general journal to kind of get that awareness out to neurologist, et cetera, who may be seeing these patients first.

Dr. Steph Dewar: So, I'm suspicious that earlier recognition, diagnosis, and treatment could potentially affect outcome and debility.

Dr. C Torok: Yes, excellent point. The mean age of onset is around six to seven-years-old and the mean time to a pediatric rheumatologist might be around eight to nine-years-old. So, there's about a two-year lag because of some of the issues I mentioned. So, the more education and awareness we get out there, the better. I had spoke at American Academy of Pediatric forums and also Grand Rounds, et cetera. I'm actually going to a patient education conference in two days. So, I try to get the word out with my colleagues as much as we can. There's only two hundred pediatric rheumatologists in the nation, and there's just about four of us that actually focus on this. So, that's why some of these things are understandable that people aren't recognizing this, but we're trying to get that more known.

Dr. Steph Dewar: So, to try and address the rarity, and what you mentioned, that the mechanisms are not really well understood, you mentioned getting blood and skin samples from patients. What do you do with those blood and skin samples in your lab? And what are you learning?

Dr. C Torok: One main component that we're looking at is a composite biomarker. That basically is, when the kids come in and they have active disease and floored. It's very red, it's white waxy, it's erythematous. We can kind of tell that that's active disease and typically we'll treat, and then they'll have the erythema, the thickness will get better, just may be left with some trace hyperpigmentation, so changes of the skin. But, then, usually, it's pretty quiet. But then, 50% of these patients recur. When they flare, it's unclear. They might just have a little bit of pink or red color change, or a little bit of itching of the skin. But, right now, even us experts, it's hard for us to tell when exactly the flare is starting, so when to restart this methotrexate, or the steroids, et cetera. So, what my main focus is, is developing a blood biomarker that will help with your clinical assessment of, "Hey. Is this patient active again? When do we start treatment?"

So, I'm trying to use the patients that have clear cut and active disease, no treatment, store their blood and get their skin samples. I follow these patients longitudinally, treat them, get them when they're inactive, collect that blood and skin and then compare the two. So, then you can define the biomarkers that are definitely elevated and predominate in the active phase of disease. So, then you can use it later to help then predict, in general, other patients, how active their disease is if you should restart therapy. So, it's a composite of the serological biomarkers like cytokines, ketokines. We've seen CXCL9, CXCL10, other interferon gamma-associated biomarkers. Then, also, in the peripheral blood looking at the cellular markers, doing flow cytometry and CyTOF, which is

just fancy flow cytometry using metal tagged ions. Then, also, looking at, in tandem, the skin. And, again, doing similar methodology, we're looking at flow cytometry, et cetera. But then, we're also doing RNA SIQ, which is looking at the transcriptome expression. And then, also, single-cell sequencing.

So, we actually can tell what cells are kind of driving these biomarkers. For example, I mentioned CXCL9 and 10 in the peripheral blood, but actually, when we do RNA single-cell Seq and look at what cells are actually different in the localized scleroderma patients from healthies, and also compared to active/inactive, the fibroblasts that have CXCL9 and 10, are actually different in pediatric localized scleroderma compared to pediatric healthy control. So, things like that may help say, "Oh, these biomarkers are of interest. One, the can help tell us if the disease is active or inactive.", or, maybe prognostic biomarkers. "Hey. This kid's going to flare down the road or have more severe disease." And also, may help for therapeutic drug targets as well.

Dr. Steph Dewar: So, this sounds like research which is very patient-based, not an animal model to help you with this-

Dr. C Torok: Correct.

Dr. Steph Dewar: ... in a very unusual disorder. So, it sounds like there might be a challenge getting adequate numbers. I'm wondering what other barriers you have to your work, like patient access. I'm just wondering if there's innovations that you have thought about or have used to help improve patients access to you.

Dr. C Torok: Yes. So, as far as patient access, I work with my social worker and we do help fly patients and provide some funding and housing there, and actually, I help connect patients. So, if I know it says "teenage female of this age" and she has linear of her leg and is maybe having trouble, then I will try to help connect them, as far as both parties agree, to other children with this and also for their parents to help. Being at the patient education conferences, I've had a ton of one-on-one time with patients and families that may not be able to physically make it here at Pittsburgh, but I'm always at the Scleroderma Annual Patient Education conferences, so they know where to find me. Then, we just develop this Kids Get Scleroderma Too, patient education conferences. The second one we're having in two days in Colorado. So, I'll be out there and meeting up with patients that may not have access to me for whatever travel reasons, et cetera. I do try to make myself accessible other ways, and that's on the clinical basis.

On the research basis, I actually am the central biorepository and lead some of the multi-center studies that I have available through CARRA. So, CARRA is Childhood Arthritis Rheumatology Research Alliance. Why that exists is not just pediatric scleroderma, but pediatric juvenile dermatomyositis, pediatric lupus, pediatric juvenile arthritis. All of these are relatively uncommon conditions, so we need to work together at the different sites so that we have the numbers to do research. Clinical research, translational research, et cetera. Therefore, I'm one of the leaders of the pediatric scleroderma group, so what I've done is, I've

developed, with some of my colleagues, such as Susan Lee at Hackensack, New Jersey, protocol where they enroll into the registry, we collect the clinical research data, the variables, et cetera from these multiple centers, and then I'm the biorepository, so they'll collect blood and ship it over. So, even if I physically can't see the patient, they're seeing another peds rheumatologist who's invested enough to collect the clinical data, the collect the blood and send it and be part of these multi-center studies.

Dr. J Williams: So, it's really critical, clearly, for these uncommon diseases of childhood to have these networks and groups of other physicians, and families, and patients who are dedicated enough to do what it takes to advance the field and develop new tools and new treatments.

Dr. C Torok: Correct. So, having the physicians onboard and collaborating, but then, also the patients and different patient advocacy through, as I mentioned, sometimes it's the Scleroderma Foundation, I have patients that they have a Facebook like Sclera Moms, but it's a private Facebook, so you have to get invited. But, they've networked themselves and then, some of them will see me and they'll say, "Oh. You need to see Dr. Torok." So, not to my doing, but they communicate as well. So, yes, it's both the patients and the clinicians kind of working together.

Dr. J Williams: Steph touched on this. For this disease, it sounds like this is the only way you're going to move the field forward. There's not any kind of small animal/mouse model or anything that people can study. Is there?

Dr. C Torok: We're starting to collaborate. One of the Ph.D.'s at Boston, so, Gillian Richmond, we just wrote an R1, so we'll see where it goes. But, they are looking at, traditionally, systemic scleroderma is more common in the adult field and I do have systemic scleroderma patients and do research on that as well, but localized is way more common. But, we've used the bleomycin mouse, which is typically a fibrosis mouse that the adult systemic scleroderma researchers use. But, basically, taking it just a day or two into the bleomycin process before the fibrosis gets too far in the skin or the lungs, is actually or kind of morphea model or localized scleroderma model. So, we've kind of just used that mouse model but just slightly adjusted it and we're starting to find skin changes and when we do the biopsy of the mouse skin it looks similar to the human localized scleroderma skin. Right now, actually, we're doing the RNA Seq and the Bulk Seq and the single-cell Seq to see if it's similar or not to our localized scleroderma patients. So, that's happening right now. Most likely, mouse model. But, we're working with it right now, but that's new.

Dr. Steph Dewar: So, you mentioned previously that you also have done some work with neurologists with the finding about the symptom of seizures in some patients with scleroderma. Are there other subspecialty collaborators that you have in your work?

Dr. C Torok: Yeah. So, I've been working a little while with Dr. Losee here at Children's Hospital Pittsburgh. Especially for the patients that have the linear facial

involvement. We call it our linear scleroderma of the head/Parry–Romberg clinic. But, basically, linear scleroderma of the head can be sub-termed, en coup de sabre, or French for "sort of the saber" because it looks like a linear line or depression on the face/skull with some alopecia, et cetera. Or, it can also be termed Parry-Romberg, which is hemifacial atrophy, so one side of the face is smaller.

In reality, these kind of overlap. They have similar phenotypes. I have children that have en coup de sabre on the left, and Parry-Romberg on the right. So, they're kind of all in the same boat. But, we see these patients in tandem together, usually on a Monday when he has his craniofacial clinic that the dental orthodontics come in as well as the craniofacial plastic surgery. We do 3D imaging of the face and then we monitor the child at the next visit, we do 3D modeling again with the camera, and we kind of overlay those pictures and if there's progression of the disease, there's a color, it will look kind of red or depressed, then we'll know, "Okay. This is depressed disease." Then, on the other management side, Dr. Losee also collaborates with myself and then Jessie Goldstein as well, to treat these patients after the therapies we mentioned like steroids, or methotrexate or CellCept and other medicine. If they're in remission and the child is unhappy with the depression on their face, et cetera, we do fat grafting. So, basically, taking some of the fat, spinning it down, and do micro-fat grafting to kind of even out the face. So, we have kind of a team here.

Dr. J Williams: Well, it's really an incredible multidisciplinary effort. Isn't it? Both in the clinical side and in the research realm. It just shows, I think for something as complex as this, that you need so many different people with different expertise to attack it. Maybe in the last couple minutes, you could just tell us a little. You're engaged in so many different things from directly seeing patients, to clinical research, to lab research, being a physician-scientist and balancing those things and how you enjoy that.

Dr. C Torok: I mean, I love what I do. I just took that UPMC survey about your quality of life. I love what I do, I love my colleagues, all my colleagues are supportive, so I have-

Dr. J Williams: That was not a sponsored statement, by the way.

Dr. C Torok: I have clinicians in my group and we work together. So, if things are stressful and someone needs to see someone in clinic, they'll say, "Hey. I'll see that patient. I know you have to go run up to the lab." So, I think it also depends on the balance in your group and how supportive your group of colleagues is. So, my group of colleagues is very supportive and also, I mentor a lot of people. So, they also understand the projects and research that I do with my fellows, et cetera. So, I would say it's a balance. I don't get much sleep, that's the reality of it, but I'm happy. I think, basically, in pediatric rheumatology, some of these kids can come in very sick, but we have advanced medications and more research keeps coming. There's more biologics that keep coming down the road, that it's very gratifying because we can help these patients and treat them. And,

hopefully, one day, actually find a cure. Maybe good or bad, then I won't have a job. But, hopefully, find a cure.

So, I think, the bottom line is, yes, I juggle a lot, but I also have great colleagues that help balance the clinical and research part as well as excellent fellows and other people on projects that are kind of doing their own thing, but I'm mentoring, so we can still keep the research moving forward, it just might be more of their ideas. I also do things with quality of life, I do a little bit of everything. So, I think, basically, just working as a team, getting collaborators, sharing those projects. I didn't mention, with the biorepository, it's not just my research, I have a ton of colleagues that say, "Hey. I have this idea. This IL12 in this disease. I want to see if it's in pediatric localized scleroderma." I collaborate with people all the time because this is a national registry meant to collaborate with people.

Dr. Steph Dewar: Well, Cassie, I really appreciate you joining us today. Certainly, I have always found your support to be a breath of fresh air. Incredibly knowledgeable clinician with some of the more challenging patients that we've run by you. I want to thank you for joining us on the podcast today.

Dr. J Williams: Yeah. Thanks to our guest, Dr. Cassie Torok, physician-scientist and director of the pediatric scleroderma clinic. We'll see you next time on That's Pediatrics.