Transcript: SickKids VS The Odyssey

Introduction

Hannah We're about to embark on one family's quest for a medical diagnosis. I'd like to invite Christina to take us back to the beginning of the journey. A journey that starts with a single question, what's happening to Daniel?

Christina Well, I just noticed that he was crying a lot, but it was a different kind of crying. He was four weeks old. He is my only son and my only child, so I had no experience really of what this felt like. But yeah, I knew something was wrong, but I was just, I think, hoping it would get better. My brother-in-law took us to the hospital, where Daniel was seen by several doctors, and it was only really then that I understood the depths of what was happening.

Hannah Can you just take us through the story a little bit? What happens next?

Christina We got to the hospital, and he was seen pretty much immediately because his breathing was very shallow. And I was sent to the waiting room, and I just sort of hung around and thought, Oh well, they'll sort it out and then I'll be able to take him home. And I went around the corner, and I looked into a room, and there was about 12 people hovering over Daniel and there were instruments being brought in. There were tubes, there was things placed on his chest—monitors and that kind of thing—and we were just told to wait.

Hannah Do you remember anything about that moment specifically that you can share with us?

Christina It was just that kind of numbing sensation of not really feeling like what was happening was real. You know, you have a baby. Never in my dreams did I think that something quite so serious was going on. And it was that sort of realization that it was something that needed this many people to look after and this many machines, and the doctor came out and spoke to us. He did say to us that had we brought him in half an hour later, Daniel potentially might not have lived. He also talked us through what had been done. They'd done some blood tests. They'd put him on some medications. And he said we need to transfer him immediately to SickKids. And then the ambulance arrived from SickKids, and the lady who was in the ambulance said: You know, this is going to be a rough ride and, you know, just be prepared.

Hannah You're listening to SickKids VS, where we take you to the frontlines in the fight for child health. I'm Hannah Bank, and this is SickKids VS The Odyssey.

Christina We went to SickKids, and by the time we got there and parked the car, he'd actually got into the ICU. And I think at that stage, I was still just hoping and praying that there would be some answers. That this would just be some really ghastly infection, and it would just be something that could resolve. But I went to sleep that night not really knowing what was going on. And, unfortunately, the next day didn't really bring much clarity. It just brought a lot more doctors to see him and a lot more tests. My son was going for CT scans and MRI scans. I was told that he'd had a stroke, and I didn't think that babies had strokes, so it was a lot to take in in a short amount of time.

Hannah What is it like as a parent to sort of live in that space even for a day or two of just not knowing? Do you remember what was running through your mind at the time?

Christina No, I think a lot of it has gone. I think I've made it go away, but I can recall just feeling it will somehow be resolved. I remember feeling very hopeful every time a new service came to see him. So I think initially it was infectious diseases, immunology and then someone said, oh, we're going to get someone from hematology and then someone from cardiology. And the cardiologist came and said, Oh, actually, there's nothing wrong with his heart. I remember feeling very relieved. Mercifully, after a day or two, there was some stability, and the CT scan that they did showed that his stroke was quite small and I was reassured that in a small baby, these things do heal remarkably quickly.

Hannah Daniel fully recovered from his stroke. But I wanted to know from Christina how often new health issues brought them back to SickKids.

Christina I would say for the first six months we were at SickKids probably three or four times a week. And then Daniel went through a period of sort of stability, really relative stability after about four or five months.

Hannah Do you know what was wrong with him at this point?

Christina No, we had no idea. A real sense of not knowing didn't really sink in until a few months after he left hospital. Because you think that you put your child in hospital, you have a lot of doctors see him. Someone's going to have an answer. Evidently, here, no one had an answer. And eventually it just sunk in but it's going to take some time and that we were in for a long journey.

Hannah When Daniel was four years old, he started experiencing new symptoms that he had never had before, including rectal bleeding.

Christina We were actually in hospital over Christmas when he was four years old, and then he was discharged, and the person whose care that he was discharged to was Dr. Muise. And he was a gastroenterologist, we were told, who had a deep interest in unknown things that come up like this.

Dr. Aleixo Muise My name is Aleixo Muise, and I'm a pediatric gastroenterologist, and one of my main interests—both clinical and research—is understanding the genetic and functional causes of very young children with severe intestinal disease.

Hannah So you have always been, since I've heard and known about you, really interested in solving medical mysteries, puzzles. Can you just tell me a little bit about where that interest was born from and how you apply it to your work?

Dr. Muise My interest comes from actual patients. And, you know, at SickKids, you know we have a lot of patients with severe disease and clinical features that don't really fit into any single box or any single disease. So, you know, my interest has been trying to connect these dots and try to understand some of these diseases to make a unifying diagnosis that really helps better treat some of our unique patients.

Hannah Because you're seeing patients with rare diseases, you are seeing patients who also are coming to you feeling extremely tired and frustrated and scared because they can't quite figure out what's going on. So I know that Daniel and Christina, when you first met them, I imagine that was sort of where they were at.

Dr. Muise Yes, so Daniel had seen a lot of doctors, and he had a lot of different problems. But when I got involved, you know, when Daniel developed inflammatory bowel disease. And I do remember that, you know, Daniel was really a great little kid. And, you know, most of our patients, you know, no matter how sick they are, they're really always upbeat and really quite brave. So I remember him being, you know, one of those patients that despite having lots of different problems and being very sick, was always very brave and always had a positive attitude. I also remember his mom and she was amazing also—like she asked the right questions and really kind of understood that Daniel had a very different or unique type of disease. I was really searching for answers what Daniel actually had. But, at that time, we really couldn't figure out what was actually driving his disease. And, really, all we could offer him were sort of Band-Aid solutions.

Hannah Aleixo helped Daniel with symptoms related to inflammatory bowel disease or IBD. But a few years later, when Daniel was around seven years old, new health issues cropped up that most patients with IBD don't experience, including extreme pain in his legs and rashes on his body. Here's how Daniel describes them.

Daniel There were days when walking was a particularly hard task and like getting into the shower, getting out of the shower. The problem was it wasn't something that was continuous. It came and went so it was a sense of frustration that you could never know what days you would have that issue and what days you wouldn't. I remember the amount of pain that I had felt, and I remembered that as the years progressed, the colour of the rashes got darker. So they started off a light shade of red, and then they gradually started getting like purplish and they started working their way up my body. And obviously the further they worked their way up, that's where the pain would be located.

Hannah Were there points where you thought I'm never going to get better or did you have a lot of hope that perhaps you would and things would change?

Daniel My parents had a lot of hope and that hope was very contagious, and it was really the fuel to keep going to be honest, because I didn't have a lot to keep me going.

Hannah When Daniel was still around seven, he met Dr. Rae Yeung. She supports children with autoimmune diseases, and she also conducts research aimed at improving their health outcomes.

Dr. Rae Yeung Daniel's probably one of the spunkiest kids I know. I know he and his family very, very well, and we've definitely been through both good times as well as bad times. And at the very, very beginning, it was bad times because his disease was very difficult to control. So Daniel had actually seen quite a number of doctors, and he had come to our clinic because of this swelling.

Daniel Dr. Yeung I remember very vividly because she was a big part of my life for a very long time, and we always went to this one room to search to see her. And I can still remember where it was. I remember her being very nice. She always found a way of calming me.

Hannah Rae was the one who diagnosed Daniel with vasculitis, a condition behind the painful symptoms in his legs. Rae helped treat Daniel on a regular basis, but she also knew a deeper issue remained hidden beneath the surface.

Dr. Yeung It's often that the most heartbreaking or difficult part of going on your journey because the families can't share with other families that my son or my daughter has X because we don't know what they have. But I really want to really reassure families that giving a disease a name or not giving disease a name does not prevent your doctors or scientists from understanding it. Daniel's case was extreme, meaning that it doesn't go away when you give just normal pain medications. We need much stronger medications to be able to make it go away. So when it gets to that point, you start thinking, is there something else unusual that can be causing this, such as something unique in their own body, something genetically, something that they're born with? And Daniel was one of these cases, where not only did he have this very recalcitrant is the word that we use—or very, very kind of stubborn disease in his legs—but he also had these other features. None of them were dramatic but when you put the whole puzzle together, so you have one little piece here, one little piece there, it was something unusual and we knew we had to get to the bottom of it because it was tremendously affecting his life.

Hannah Both Rae and Aleixo had been studying Daniel's case very closely on their own. But they also started talking to each other about their thoughts and theories.

Dr. Yeung A journey that is very, very common to children at SickKids is that they come with an unusual symptom. It is rarely, if ever, confined to one organ system in the body, and the lovely thing about SickKids is you can walk down the hall and you can ask an expert in another organ system. You can ask an expert in the lab next to you. And I think this type of grassroots collaboration, this type of dialogue—hallway dialogue—as well as a formal dialogue is something that you can't find anywhere else. So it's exciting because you hear a colleague give a talk, you get an idea. You run into them in the hallway, you get an idea. And the idea actually was that often children with inflammatory diseases of their blood vessels, inflammatory diseases of their joints and inflammatory diseases of their bowel were very, very similar.

Dr. Muise Some of our patients do have similar symptoms or overlapping symptoms, so we've worked closely with Dr. Rae Yeung on a number of patients, including Daniel.

Dr. Yeung I am in no way an expert in the gut, and Dr. Muise is in no way an expert in the blood vessels. But I think we work very, very well together.

Hannah In 2014, when Daniel would have been around eight years old, both Rae and Aleixo—along with many other colleagues at SickKids—collaborated on a major project to explore the genetic basis of IBD and similar conditions using advanced DNA sequencing techniques. Aleixo wanted Daniel to be included in that research because, like Rae, he also felt the young boy's genes held the key to unlocking a diagnosis. I asked Aleixo what raised his suspicions.

Dr. Muise Probably the most important thing was, you know, the very young age where he presented as an infant with a severe disease, especially having a stroke, which is very rare for any of our patients. And also he really had, you know, this sort of syndrome of different clinical features—so such as his rash, his vasculitis, his immune problem—really pointed out that it was a single gene that was causing this sort of broader group of diseases for him. Until recently we didn't really think of, you know, inflammatory bowel disease or IBD as really having a genetic cause to the disease. However, in a study in my lab, we were able to show that three percent of all the IBD patients—regardless of how sick they were, how old they were at diagnosis—actually have a genetic cause. And this is really important

because understanding the genetics helps us to treat those patients with the rare genetic diseases.

Hannah So just to recap, for Daniel, you were, you knew that you were probably looking for something new, something different. You didn't necessarily have an idea of what that might be. So in some ways, you're just sort of casting the net quite wide and seeing what's coming back. Is that sort of the idea here?

Dr. Muise We knew we had a genetic problem, but we couldn't figure it out. And people had looked at the known things, so they use different genetic approaches and they did not find any known genetic cause. We had funding actually that allowed sequencing of both Daniel and his parents. And this gives us really an unbiased approach. So instead of looking at, you know, one or two things that could cause disease, this is looking at every single different gene to see if we can identify the problem.

Hannah I wanted to hear from Christina what she thought about the idea to examine Daniel's genes at the time.

Christina Obviously we signed up because we needed to know, and I imagine it would have taken a lot for Dr. Muise and his team to really push that through for Daniel. But he did say that this is probably going to be the one thing that will explain everything to us. And in those days, it took one year for them to do everything. So, yeah, we had to wait for a long time.

Hannah SickKids breakthroughs are only possible with the incredible support of our donors. That's why we're proud to recognize CIBC as the premier partner of the SickKids VS podcast. The bank and its team members care about making a difference. CIBC has championed SickKids for over 30 years and is the largest corporate supporter of the SickKids cancer sequencing program. CIBC also generously supports SickKids through CIBC Miracle Day and an active employee giving and volunteer program.

After that year, do you remember sort of having that conversation once the results came back?

Christina Oh, I'll never forget it. Daniel was having the regular monthly treatment. That's where Dr. Yeung would come and see him quite often. We'd gone in, and she was very excited.

Dr. Yeung I remember running to their room, OK, telling them: I think we found something.

Dr. Muise I do remember Daniel's discovery quite well. And the minute that we actually saw his results, we knew that we actually had a slam dunk and that the gene that we discovered was causing his disease. Using the same funding and the same grant, we were able to identify a second family that had symptoms that were very similar to Daniel, but not as severe, and they had mutations also in this in this same gene. So when you have two patients that have mutations in the same gene with similar defects, this makes it much more likely that this mutation or this gene is causing disease. You know, we were excited for Daniel and his family but also excited at the possibility of defining a brand new disease that could really help some other patients, like Daniel.

Hannah When people ask Daniel, like, what do you have? Is there sort of like a name that's born out of some of these discoveries?

Dr. Muise You know, they used to be able to name diseases after the the doctors, but that doesn't happen anymore. Daniel would love for it to be called Daniel's disease. Often, once we have two or three patients, then it becomes the medical literature as a real disease. And in this case, it would just be ARPC1B deficiency.

Christina He's basically deficient in this particular protein, and it was the tiniest thing. They said he actually has none of this protein that you need in order to have a functioning immune system.

Daniel That diagnosis had represented and meant everything we had wanted, all in one word, really.

Hannah How did your parents react, Daniel, when they learned the news?

Daniel I remember them standing outside the room and they were very happy. I remember, I remember the joy they had on their faces. And it was something quite immeasurable, really.

Christina It was pretty amazing, actually, and I'm so glad looking back. It was so clear to me that both Dr. Muise and Dr. Yeung were really fully, completely behind finding out what was wrong with Daniel. They were so devoted to that cause.

Hannah How wonderful to feel like you had two people who were hopeful and who worked so hard to be able to discover this, this diagnosis. So you get this news, you find out that there's a protein that he is not producing. What's next?

Christina In the same conversation, we were told that it would be a bone marrow transplant that resolves it. So whilst there was this kind of joy attached to finding out what was wrong, there was also this slight worry about a bone marrow transplant. I remember wondering whether we would get a donor. Is he going to be okay through this process? We just shifted our focus to now finding a right donor for him. And then Dr. Yeung suggested that she would actually be happy to consider his parents. So in the end, it was me. I had to go and be tested, and it turned out that I could actually be his donor.

Hannah Soon after, Daniel underwent the bone marrow transplant. He was 11 years old at the time.

Dr. Yeung What you do is you dampen down the mutant bone marrow and you basically put a brand new set of bone marrow cells that are unaffected, that are healthy and you, you basically give it a good home and you hope that they grow really, really well and that they're going to grow even better than the original cells. And in Daniel's case, they did. And what they did is because they not only brought in a brand new bone marrow, but a brand new bone marrow that had a normal copy of this gene, which then made a normal copy of this protein, which then was able to help white cells and platelets do their normal things and basically cured him. It was incredible.

Daniel It was quite hard to believe, actually, because it's something you waited for for so long that when it actually does happen, it's something that is very surreal at the time.

Hannah And how long before you started to see any sort of change in Daniel?

Christina Well, that took a while. And then, interestingly, it was Dr. Yeung who came to see him. And I remember being outside the room with her in the corridor, and I said, Is that it then? Is it done? Is it done? And she said yes. And I never forgot that feeling. I, yeah, I cried. I said, Is that it, he's cured? She said, yeah, and it was just. Yeah, that was an amazing feeling. That was elation. That was everything.

Dr. Yeung I remember him running through the hallway on the eighth floor in the hospital and flying into my arms to give me a big hug because he was so happy. I mean, it was, it is imprinted in my mind.

Hannah And Daniel, do you remember hearing those words that you were cured? Do you remember what that was like?

Daniel I remember a sense of disbelief, and I remember a sense of normality, really. I remember coming home and it being very surreal. Now that I had been cured, everything, like my freedom was back. Everything I've been wanting to do and needing to do for so long, I could now do. So like I could now go skating. I could now play hockey if I wanted to. I could have all these options.

Hannah These days, more children at SickKids have access earlier in their journey to genome sequencing and other precision diagnostic tools. Aleixo also mentioned there was at least one other child with the same condition as Daniel when the genetic discovery was made. I wondered what else had changed since then. So I asked Aleixo and Rae for an update. Has that work helped or informed any of the other cases?

Dr. Muise Around the world, there's been a large number of patients—over 100 patients—that have been diagnosed with the same disease, and many of them have been treated and cured through through bone marrow transplant. So, again, studying one, you know, very rare patient like Daniel has helped many patients around the world for sure. I would 100 percent love if every single patient that had a, you know, unique disease, or even not that so unique, would be sequenced because they probably could treat a lot more patients better if we had that data.

Hannah It took about a year before Daniel's genetic sequencing results came back. How is that different today?

Dr. Yeung So this is really the beauty of science, is that the technology behind sequencing is leaps and bounds ahead right now. So not only the technology, meaning the machine and the reagents can sequence much faster, but access to the technology is at a different level than it was when we had to work with Daniel. Almost, I would say, every week in my clinic, we need to ask some specific questions about their genes. We'll get it back probably in about a month. So not a year, but about a month, which is fantastic.

Hannah Dr. Yeung, I was hoping you could talk a little bit about the importance of rare diseases.

Dr. Yeung Yeah, absolutely. I think rare diseases are nature's way to teach us a lesson. I think it's important to think of it that way. They may be rare, but they're incredibly not rare number one to the individual in the family that's being affected. But the most important thing when we think about rare diseases is that by learning lessons in somebody who has an extreme version of a disease—so in what we talked about earlier for Daniel's case, what you do is you've uncovered that one gene that led to that one protein. That one

protein interacts with hundreds of other proteins that actually now drive this pathway. And with that, we now have opened up an entire area of research for much more common, much less severe types of disease. And that leads to advances in therapy.

Hannah Today with his medical odyssey behind him. Daniel is fully recovered, meaning no more pain, no more rashes and no more treatments at SickKids. Daniel turns 16 this year. Can you tell us some of the activities that you enjoy?

Daniel I really enjoy photography. I take a lot of pictures. I enjoy like waking up early and just taking photos of the sunrise and the sunset when it's late and it's really nice and I enjoy hanging out with the family.

Hannah Christina, other parents might be going through the very same thing in a different context, meaning they don't know what's wrong with their child. Is there anything that you feel that you would like to say to those families?

Christina I would say, don't stop hoping. Don't stop praying. There is changes happening in the medical world on a practically daily basis. And it's pretty astounding to see simply from a genome sequencing perspective. Things are advancing in such an amazing way. And there is always, always hope, and you're in such amazing hands at SickKids.

Hannah From SickKids Foundation, this is SickKids VS. Thanks for listening. If you want to support work like this, visit SickKidsFoundation.com/podcast to donate. And if you like this podcast, please subscribe and rate us on Apple or Google Podcasts, Spotify or wherever you listen to SickKids VS. SickKids VS is produced by me, Hannah Bank, Neil Parmar, Jasmine Budak and Gillian Savigny. This episode was written by Neil Parmar. Sound design and editing by Quill. Production Support by Ayesha Barmania. For behind the scenes extras and show notes visit SickKidsFoundation.com/podcast.