Your Complex Brain – Season 3 Episode 5 – Erasing the Stigma of Neurofibromatosis

Dr Suganth Suppiah 00:01
[Your Complex Brain theme music] The general public does not really well understand what this condition entails. A lot of times there's a fear that this could be a transmissible disease, so that's a common misconception and that can lead to a lot of self-consciousness in the NF1 patient population, and also impacting their sense of self and their quality of life. [music continues]

Heather 00:36

[music continues] This is Your Complex Brain, a podcast all about the brain, the diseases that impact it, and the path to finding cures. I'm your host, Heather Sherman, and I have the great pleasure of working alongside the team at the Krembil Brain Institute in Toronto, Canada, a leader in brain research and patient care. In each episode, we'll take you behind the scenes into our clinics and research labs to meet the game-changers of the future. We'll empower you with the latest research to help you take charge of your own health. You'll also hear from people who are living with brain disease, as well as their loved ones and the care teams who support them. Join us on a journey to unravel the mystery of your complex brain. [theme music continues then fades out]

[gentle electronic music] Have you ever heard of a genetic condition called Neurofibromatosis or NF? Well, I hadn't either. In fact, most people haven't. It's actually one of the most common genetic disorders, affecting about 1 in 3,000 people, globally. NF causes different types of tumours to form in various parts of the body. Because so little is known about the condition, it's often misdiagnosed or not diagnosed at all.

Today, we're going to talk about the exciting research happening in the field of NF. But, for many people living with the condition, the stigma is often as challenging as the illness, and for Dr Ryan Thomas, treating patients who are living with neurofibromatosis is very personal. [music continues then fades out]

Dr Ryan Thomas 01:59
[bubbly, pensive electronic music] My name is Ryan Thomas. I'm a physician working at the Elisabeth Raab Neurofibromatosis Clinic at UHN , and I, myself, am a patient living with the condition. I was diagnosed in my late twenties, so it wasn't an early or childhood diagnosis, which other patients may have experienced. From early childhood, I had always noticed a few lumps and bumps and café-au-lait macules – light brown, sort of spots on the skin that look like birthmarks. However, depending on whether it's a child or an adult, there's a certain number and a certain size that can be one of the clinical manifestations of neurofibromatosis.

But it never really amounted to anything, and I, otherwise, felt fine. It wasn't until my late twenties, when my very dedicated family physician used a stethoscope, said that she couldn't really hear a lot of movement in the right side of my chest, and then decided to organize some follow-up testing which eventually led to the discovery that I had a very large tumour in my chest and that's why she wasn't able to hear anything. And I eventually needed to have surgery to have that dealt with.

[music continues] It was a big shock, especially because it was both discovering the large tumour, as well as the diagnosis of neurofibromatosis at the same time, and then all of the investigations, appointments, and planning that then went into it, it was sort of a life-changing experience. I was in the middle of my

family medicine residency in Australia and my wedding was also a few months away, as well. To, then, have to be faced with not only the diagnosis but the need for fairly urgent surgery, it sort of put everything else on pause. It was a fairly serious finding and, from what, you know, I could initially see, it may have been something that may not have given me a lot of time left.

[music continues] After the initial diagnosis and discovery, I had to have, you know, several sets of imaging, biopsies, scans. I met with a few different specialists and all of that went into sort of planning for the surgery, which happened about two to three months after the initial diagnosis. And then, it took about six months for me to recover from the surgery because it was quite an extensive surgery that was needed.

Because of my upcoming wedding and the fact that my family was in Toronto, I had decided to have the surgery back in Toronto. While I was in Australia, I had to undergo what was called a high-altitude stimulation test to see whether it would be okay to fly with such a large tumour in my chest. I had the surgery prior to the wedding. It was about two months before, so it was just enough time to, you know, allow me to sort of heal enough to be able to stand up. [music fades out]

[glitchy electronic music] Six months after the surgery, I was able to resume my training and eventually complete it, and in terms of the types of treatment, I do have regular monitoring with MRI; that's kindly organized through the Elisabeth Raab NF Clinic. I see the specialist there once a year, myself, and that's just been to track any sort of recurrence of the tumour.

[music continues] It's really helped me, being able to relate to patients to know what it's like to live with it on a day-to-day basis, how the tumours feel, how it feels like to go for regular scans, what's involved, how to interpret the pain. I do see that a lot of patients are quite grateful when I'm able to share that with them because they may not often meet another person with NF1, as well, so they really do seem to appreciate that I can understand what they're going through. [music fades out]

[upbeat electronic music] There are a few different types of neurofibromatosis. Most commonly is neurofibromatosis type 1, and there is another related condition called neurofibromatosis type 2. However, that's been reclassified as NF2-related schwannomatosis, and there's another group of conditions called schwannomatosis. All of these conditions have some overlapping or similar conditions, but they're actually considered genetically and clinically distinct conditions with their own treatment, their own symptoms, as well.

At the clinic, we see patients with NF1, NF2 and schwannomatosis. There is a lot of stigma associated with NF1, especially as one of the symptoms are cutaneous neurofibromas or lesions on the skin. So this will lead to sort of a lot of people in the general public not knowing what it is. Some people may think it's infectious; some people may not understand what it is. I've had patients tell me that people have just come up to them in public and just asked them. It's really unfortunate that there isn't a better understanding in the general community about it, given how common it actually is.

[music fades out] When I was first diagnosed, I only knew a bit about the condition, myself, and it did feel very isolating. Thankfully, there is an NF clinic here in Toronto. There was one in Sydney, in Australia where I was initially seen, as well, and it really made me feel very comfortable and at ease knowing that there were specialists in the area that knew and understood the diagnosis and how to help me, and that's something that I'm thankful to now be a part of, as well. [music fades out]

[uplifting electronic music] While it can run in families and some patients may have a family member that's affected, for many, they're the only one that they know with neurofibromatosis, so even being able to come and see other patients in the waiting room and see someone else with the condition, many patients have just found that very nice and, commonly, they'll just break out in conversation amongst themselves, and then even be able to speak to me. A lot of people really appreciate that.

To have a condition that's genetic, which is therefore, you know, being told that there's no cure, to then be given some hope that there are treatments to both help some of the physical manifestations as well as pain, and it gives me a lot of hope for the future that there are now drugs that are available to treat, you know, certain cases of people with NF1. There's a global conference as well that happens, so it's very exciting. It's something I hope to, you know, be a part of in the future.

[music continues] There is a lot of momentum in the field of NF now – a lot of excitement, which gives me hope for the future that we'll all be able to better benefit and treat patients, to not only help them with, say, pain, weakness that may associate from nerves that are being compressed, but also from the physical manifestations, as well. [music fades out]

[bubbly electronic music] It's been extremely rewarding that I've been able to help and work with other patients with it. It's been able to help me use the diagnosis that I have to help other patients and, if I can share some stories and relate with them and make them feel better, then, I mean, that feels really great to me. And it's because of Dr Vera Bril that had, you know, invited me to join the clinic and I'm thankful for the opportunity and, you know, thankful that I can help other people with the condition.

[music continues] My message to our patients is, "Don't give up hope. We understand you. If you have concerns, then we're here to help you. New research is evolving and we're hoping to be able to better treat and understand this condition as time goes forward."

Heather 09:40
[Your Complex Brain theme music] What an incredible and inspirational story. My guest today, Dr Suganth Suppiah, has always been fascinated by neuroscience. Back in high school, he wanted to be a computer programmer, but now the surgeon scientist at UHN's Krembil Brain Institute and Assistant Professor at the University of Toronto is on a mission. His goal? Researching the molecular pathways of neurofibromatosis and treating patients who are living with the tumours associated with the disease. Doctor Suppiah also leads the nerve surgery program at Canada's only adult neurofibromatosis clinic, which is based at UHN. Thank you so much for being here today. [music fades out]

Dr Suganth Suppiah 10:30
Thank you for an opportunity to present some of our work in our clinical and research neurofibromatosis programs.

Heather 10:37
Absolutely. So, neurofibromatosis, this is a word and a condition that I think many people probably are not very familiar with, so can you tell us a little bit about it, and also, how common is it?

Dr Suganth Suppiah 10:47
So, neurofibromatosis is a family of genetic syndromes that predisposes patients to developing numerous tumours. Although it is not well understood, it's actually a relatively common condition. So, neurofibromatosis type 1 is about 1 in 3000 individuals, while neurofibromatosis type 2 and

schwannomatosis are in about 1 in 35,000 to 1 in 40,000 patients. So it's a relatively common condition. We just may not easily identify it and, in the general public, might not be well understood.

But this tumour predisposition syndrome causes these patients develop hundreds to thousands of nerve tumours along the nerves and the central nervous system and into the extremities, as well, and so can cause significant medical comorbidities, and also mortality from cancerous tumours.

Heather 11:37
So this is one of the reasons why we wanted to talk about this condition today. As you said, it's relatively common, but many people may not understand what it is or may not even know that they have it. So, before we get into some of the details about, you know, exactly what patients experience, what is the difference between type 1 and type 2, as you mentioned?

Dr Suganth Suppiah 11:54
So, neurofibromatosis type 1 is caused by a genetic mutation in the NF1 gene on chromosome 17, and this patient population develops hundreds to thousands of nerve tumours called neurofibromas along, again, as we talked about, throughout the central and peripheral nervous system. And then, they can also develop other tumours in various aspects of their body as well, including gastrointestinal stromal tumours, optic pathway gliomas, and they get a lot of skin manifestations, including multiple, again, hundreds of thousands of cutaneous neurofibromas, which are tumours on the skin, and also axillary freckling. So, that's the most common symptoms you'd see in NF1.

And then, NF2 or neurofibromatosis type 2 is caused by genetic mutation – the NF2 gene on chromosome 22. And similarly, this patient population would develop tens to hundreds of schwannomas, which is another type of peripheral nerve tumour like neurofibroma, but just a little bit different from a histopathological standpoint. And almost 100% of patients would develop tumours along their hearing nerves bilaterally on both sides. In this patient population, deafness becomes an issue over time, as these tumours grow and cause damage to the acoustic nerve.

So that's their most common presentation, but they are also can develop schwannomas along the spinal cord and in the peripheral nervous system, as well. And then, finally, schwannomatosis is a more recently-described condition which was previously known as neurofibromatosis type 3, and there's two different genes involved in this condition called LZTR1- and SMARCB1 and, again, in this population, they develop schwannomas along the peripheral nervous system. But, unlike neurofibromatosis type 2, they don't develop the tumours along bilateral hearing nerves, so the schwannomas tend to be more concentrated in their peripheral and spinal systems.

Heather 13:40
[gentle electronic music] So, it seems like a very complicated disease to treat and to study. Can you tell us about that? Like, what makes this disease so complicated?

Dr Suganth Suppiah 13:49
The number of tumours involved plays a major challenge, especially when trying to figure out which tumours are growing, which ones are symptomatic. It's not always very easy and cut and dry to figure out which ones would benefit from treatment.

Second of all, it's the various different organ systems that are involved. So, as you can imagine, tumours developing in the brain would need a neurosurgeon involved. Tumours along the spine would need a

spinal surgeon. And then, the peripheral nervous system would need peripheral nerve surgeons. But also, if the tumours are growing in the abdomen, then general surgery would need to be involved. So there's multiple teams or surgical and medical teams that are involved to try to manage this patient population. And then, also, outside of the tumours, they can develop other medical comorbidities associated with their condition and, for that, you know, neurology, geneticists are involved and closely monitoring these patient groups. [music fades out]

So the challenges arise from both the complexity of the tumours involved, the risks of malignant transformation where you have to monitor thousands of tumours to see which of those thousands where one may undergo malignant transformation, and then also the number of various organ systems involved that might need surgical interventions. So, it can be a bit of a challenge from just one physician taking care of it, and that's one of the advantages of having a multidisciplinary adult neurofibromatosis clinic comes in to help provide more comprehensive care for this patient population.

Heather 15:10
Which it sounds like they need. So, taking it back a step, we talked about the fact that this is a more common genetic disorder than people realize, yet people may not realize they even have it. So, what are the symptoms that might even send someone to their family doctor in the initial stages?

Dr Suganth Suppiah 15:26
So, typically, early on in the child's life, their pediatrician or physician might notice these café-au-lait macules are actually freckling, so these skin pigmentation changes that might suggest the possibility of an underlying neurofibromatosis condition. And so, for those kids, they undergo genetic testing to confirm or exclude the diagnosis of neurofibromatosis.

And then, if, at that stage, it's not identified and sometimes it's not, usually later on in adulthood, they start developing neurological symptoms associated with whichever nerve or central nervous system that is affected by the tumour. So patients can present with shooting, burning pain along a single arm or multiple extremities with new weakness, numbness, tingling. And then, if it's in the spinal cord, they can have difficulty with walking or fine motor skills. And then, if it's in the brain, patients can present with hearing loss or other balance problems and other symptoms associated with the mass effect or the compression of the tumour along the brain, spinal cord, or peripheral nerves.

Heather 16:29
It sounds like these are a lot of symptoms that can also be associated with other neurological diseases. So, is it often the case that many of these patients might even be diagnosed later or misdiagnosed completely?

Dr Suganth Suppiah 16:40
That's correct, and that's one of the challenges for the primary care physicians and the healthcare professionals. It's the vagueness of the symptoms that could be attributed to other neurological conditions and the lack of expertise in the field outside of these academic centres where, you know, primary care physicians or family doctors might not have had much exposure to this condition and not had experience with it. So, oftentimes, patients can be worked up for other conditions until, eventually, an MRI is done where it shows one or two of these tumours and then they get finally referred to our clinic for assessment, both for genetic testing and for surgical or medical management of their tumours.

Heather 17:21

And so, that leads me to my next question, which is really about the treatments that are available for patients. But, before we get to that, I wanted to talk a little bit about what some patients describe as the stigma associated with the condition because of some of the external tumours and other things that are associated with the disease, but also because it affects so many different systems and so many different organs. So, having treated as many patients as you have, what do you hear from them about what it's like to live with this condition and about the stigma that they face?

Dr Suganth Suppiah 17:46
One of the major challenges is the physical stigma of having multiple cutaneous neurofibromas, and when the general public does not really well understand what this condition entails, a lot of times there's a fear that this could be a transmissible disease that, if you touch the person you can get these continuous neurofibromas developing. So, it's a common misconception and that can lead to a lot of self-consciousness in the NF1 patient population. And also, you know, impacting their sense of self and their quality of life and ultimately their psychosocial well-being and I think that's a major concern and one of the challenges, again, with the current OHIP system—our provincial healthcare system—is that treatment of cutaneous neurofibromas is considered a cosmetic procedure which, given the amount of social stigma associated with this condition and also the psychosocial impact of having multiple skin tumours, makes it a major challenge, so it's hard for this patient population to identify physicians that are able to treat this and try to help them improve their quality of life, in general.

Heather 18:50
[bubbly electronic music] That is really unfortunate. What else do patients tell you about just their life and some of the challenges that they face on a daily basis?

Dr Suganth Suppiah 18:58
The pain that they get from the numerous tumours along the peripheral nerves, and sometimes, with surgical management, it's not always feasible, considering they may have 1,000 tumours or more than that, and not all these tumours can be operable, and therefore, they might have to try to live with chronic pain which can be, again, very debilitating, and very limiting in their function.

And then, there's also the neurological impact of these tumours, which can include weakness, numbness, tingling, balance problems, and bilateral hearing loss. So, a lot of these tumours can cause significant neurological impact that limits their overall function and their ability to integrate into their job or, you know, into their schools, and makes it a major challenge from to kind of deal with the challenges associated with the condition, and that could be a major factor in overall quality of life. [music fades out]

And given that, you know, from healthcare system perspective, there's not a lot of supports for this condition and for this patient population, it can often be a challenge for them to find other people who have gone through the same experiences, and they can often feel alone when, in fact, you know, this condition is relatively common and there's a big population that people can lean on and try to learn from each other's experiences. But there's no unified kind of group – patient advocacy group to help support this patient population.

Heather 20:24
And that's got to be hard to hear as a clinician, because I know that you spent a lot of time with these patients.

Dr Suganth Suppiah 20:28
That's correct. It's always a challenge because, you know, you see, on a daily basis, what these patients have to go through and, as a surgeon, we have very limited tools available to us to help treat this. As we mentioned, not every tumour is surgically respectable and, even if they were, it's next to impossible to resect thousands of tumours while maintaining the patient's quality of life.

So, eventually, it might not be a surgical disease, but a lot of work needs to be done up from a research point of view to identify the factors that are driving the tumour development and whether or not we can try to stop this with targeted therapies, systemic therapies that would treat every tumour at once or a major subset of these tumours. So, I think a lot of work needs to be done and one of the major challenges is also the amount of funds available for research and also the amount of researchers that are looking to try to solve the problems associated with neurofibromatosis. So there's a limited scientific community that's focused on neurofibromatosis research, and there's also a limited physician community that's dedicated to managing neurofibromatosis.

Heather 21:35
Yeah, I know you're kind of a unicorn in this field, in that you work up both on the research side and on the clinical side.

Dr Suganth Suppiah 21:40
That's true, but with Dr Zadeh developing the Multidisciplinary Adult Neurofibromatosis Clinic, that's been one of the major steppingstones to improving the clinical management of neurofibromatosis, but also driving more interest in both clinical and research advances in management. And, although we're the only adult neurofibromatosis clinic in Canada, there's a couple of centres in the US, as well, that now we're partnering with to increase the exposure, increase the collaboration across North America to, again, improve the quality of care provided for neurofibromatosis patients and make sure that we're trying to make sure that we're driving the advances in care.

Heather 22:23
Well, as you say, I mean you're building on a lot of the momentum that's happening in this field right now. So, tell us about some of those research advances that you have been working with, specifically, but also that are happening, overall.

Dr Suganth Suppiah 22:34
Over the past 10 to 15 years, there's been a huge drive to identify the molecular drivers of tumour development across multiple tumour families, and we've leveraged those technologies to understand what drives both tumour development and malignant transformation in neurofibromatosis-associated tumours.

[gentle electronic music] So, while I was doing my PhD with Dr Zadeh, at Princess Margaret, we looked at the full spectrum of nerve tumours associated with neurofibromatosis and identified two distinct mechanisms by which tumours transform into malignant peripheral nerve sheath tumour—MPNSTs—and we've hopefully identified two potential targets for targeted therapy that may hopefully, in the future, lead to clinical trials and may impact the overall outcome associated with these malignant tumours.

And preclinical studies, with these potential drug therapies, have shown that there is impact, and so now the next stages would be to develop clinical trials. And, along those lines, not from our centre but

across multiple centres and with our Adult Neurofibromatosis Clinic's involvement, there's also been approval of new drug therapies for inoperable neurofibromas called plexiform neurofibromas, and this is the first drug that's ever been approved for neurofibromas and benign nerve sheath tumours, so I think this is, again, a great stepping stone for their drug development and showing that there's been a more-increased concerted effort to study this condition and try to improve quality of life through new drug development. [music fades out]

Heather 24:09
I know you were also telling me about liquid biopsies. How does that factor in?

Dr Suganth Suppiah 24:13
So, that's another research avenue that we're exploring, in conjunction with Dr Zadeh, and our lab, as well. So, liquid biopsy again, Dr Zadeh has been one of the pioneers in developing this technology to identify brain tumours based on sampling of the blood and looking for tumour DNA in the blood and trying to profile it with new, current technology. So, it's a minimally-invasive methodology to identify and sub-classify brain tumours. And, given that we have thousands of tumours in the neurofibromatosis population, this is a great avenue to explore and develop, to be able to monitor patients' blood for potential DNA of malignant tumours or MPNSTs and identify tumours before they become symptomatic, having another tool outside of an MRI to identify tumours before they become malignant, or as they're undergoing malignant transformation, and therefore provide earlier management and hopefully improve the outcomes associated with this terrible disease.

Heather 25:12
So, earlier intervention, more-personalized medicine in the long run, and hopefully better outcomes.

Dr Suganth Suppiah 25:18
That's correct.

Heather 25:19
So, I guess, for you, being in this field at this time is kind of exciting. I mean, there's a lot happening, as you say, in the last 10 to 15 years, and you're one of a very small handful of researchers and surgeon scientists in the world who are working in this field. So, what is it that drew you to neurofibromatosis in the first place, and what do you find about it that's rewarding?

Dr Suganth Suppiah 25:39
I would like to say, you know, working with this patient population to see their tenacity, their courage, their dedication, and their fortitude to move forward with all the neurological impacts of the condition is quite impressive, and I can't imagine doing anything else but trying to improve quality of care and also just quality of the patients' lives. And just working with the Adult Neurofibromatosis Clinic, working with multiple sub-specialties, and just seeing, you know, how care evolves over time and just being able to try to treat the most pressing issues with this patient population, I would say it's the most-rewarding aspect of being in this unique setup, but I think there's also a long way to go and, hopefully, over my career, we could develop more advances.

Heather 26:27
[upbeat electronic music] And maybe a cure. That would be the holy grail.

Dr Suganth Suppiah 26:30

That's the hope.

Heather 26:32
I know we started off this episode talking about the fact that you originally wanted to be a computer programmer and you sort of found your way to neuroscience and neurosurgery. How do you feel, being here at this stage of your career? I mean, did you imagine, as a high-school student in Toronto that you would one day be a neurosurgeon and a scientist here at UHN?

Dr Suganth Suppiah 26:51
I don't think I expected, you know, where I'd be. I always had the goals of becoming a neurosurgeon back in high school after I decided to switch fields from computer science and computer programming. But, that being said, I don't think I would have anticipated being here and I'd have to say the journey was long and circuitous, but all the different opportunities and mentors that have paved the way to get me to where I am, I'm definitely thankful for. And just try to keep your head up and keep moving as new opportunities arise, and just keeping your eyes open for where there are gaps in care where you can provide your most meaningful contributions, I would have to say is the most important thing to consider because, again, you know, you never know where life is going to lead you, but there are a lot of opportunities and just try to see where you can make the biggest impact.

Heather 27:39
Amazing. Thank you for all that you do for patients and all that you do on the research side to advance these discoveries. They're much needed. Thanks for being here today.

Dr Suganth Suppiah 27:48
Thank you very much. [music continues then ends]

Heather 27:54
[Your Complex Brain theme music] Thank you to Dr Suganth Suppiah for joining me on the podcast today and to Dr Ryan Thomas for sharing his personal story. If you'd like to hear more from Dr Thomas, head to our website—uhn.ca/krembil—and click on the show notes for today's episode.

[music continues] This episode of Your Complex Brain was produced by Jessica Schmidt. Dr Amy Ma is our executive producer. Thanks also to Kim Perry, Meagan Anderi, Sara Yuan, Liz Chapman, and Lorna Gilfedder for their production assistance.

[music continues] If you enjoyed this episode of Your Complex Brain, please tell your family and friends, and don't forget to leave a rating and review on your favourite podcast listening app. We'll be back in two weeks with another exciting episode. Have a great day. [music continues then ends]