



PODCAST

The National MS Brain Bank: Advancing Research

Episode 173 – Podcast Transcript

[(0:00)] [intro music]

[(0:24)] Stephanie Buxhoeveden: Welcome to the Can Do MS Podcast. I'm your host, Stephanie Buxhoeveden. I live with MS and I'm also a clinician and MS researcher. Today, we're excited to welcome our guest, Dr. Claire Riley, who's the Karen L. K. Miller Associate Professor of Neurology at CUIMC and co-director of the Columbia University MS Center. She's here to talk to us about her MS research. Thank you for being here, Claire.

[(0:47)] Dr. Claire Riley: Thank you so much for having me, Stephanie. It's a real pleasure.

[(0:51)] Stephanie: Awesome. First, can you start by telling me about your role and how you became involved with the National MS Brain Bank?

[(0:58)] Dr. Riley: I'm happy to. So, we, uh, responded to a call for proposals from the National Multiple Sclerosis Society. Uh, this was back in 2019 and the funding, um, we were lucky enough to be selected and the funding came through in 2020. And, uh, as you might recall, there are quite a few things going on in 2020 both in medicine and in the world, so it was sort of a hard time to start anything new, um, but, uh, that is sort of where when we launched. And, um, so my role in the National MS Brain Bank is that I direct the prospective recruitment of the cohort and the characterization of that cohort. This gets to sort of what sets our Brain Bank apart from other projects, um, in that we really want to understand the clinical history of the individual who goes on to donate her or his brain. And so, we engage with people while they're living with MS, get them involved, understand what's happening with their disease, and then when the time comes and at the end of life, they donate their brain and spinal cord to our project, we can really contextualize that donation and understand that person's particular disease.

[(2:15)] Stephanie: That's really interesting. Can you explain to our listeners why studying central nervous system tissue is so important to MS research?

[(2:24)] Dr. Riley: One of the things about MS, and imagine you know this or even experience it personally, but the disease has an incredible range of expression. It's very heterogeneous. It's not the case that there is a predictable progression from

onset to, um, to conclusion of the disease at the end of life. There's really a tremendous amount of variation. And we have often wondered why that is and I would argue that our tools to measure the disease, um, range from these clinical assessments and neurologic exam you might get when you go to the doctor, um, to the, you know, blood testing or spinal fluid assessments that will, you know, look for blood-based or fluid-based biomarkers, uh, the very successful biomarker of imaging, MRI, and PET-based imaging. So, other advanced imaging modalities. But- but tissue is, um, part of that continuum and we think that, you know, while- whereas we see this heterogeneous expression of disease that perhaps the tissue has a story to tell us that- that the imaging and the blood-based biomarkers and the physical exam is- is not fully elucidating. So, we really want to glue together and demystify that, um, that gap between what's happening in the tissue, um, and then the outward expression of the disease.

[(3:55)] Stephanie: Yeah. And I study blood biomarkers, um, epigenetic markers, specifically, and what's challenging about studying MS is you have everything outside of the central nervous system and then you have this blood-brain barrier that separates the CNS. And so, you're taking peripheral blood but it's not necessarily reflecting what's going on on the other side of that blood-brain barrier, but it's hard to study that in people, and especially if people are alive. It's- you can't really take samplings of their brain and upper spinal cord. Um, so I think this Brain Bank is so unique and so exciting because it's one of the only ways that we, as researchers, can actually look at the affected tissues in humans, in people with the disease, and I think it's just amazing work that you're doing.

[(4:43)] Dr. Riley: I couldn't agree more. I mean, you know, blood-based biomarkers are obviously quite important but we're sampling a different compartment than probably where most of the action is. Not to say that the periphery is not important, I think it's very important and we can learn a lot from it, and obviously, there's a crosstalk between the central nervous system and the periphery. But, um, there's something very compelling about getting to ground truth and I think that when you're looking at the function of the brain and spinal cord probably that ground truth is within that- that territory. Um, and so- so we're really trying to build a resource that will allow researchers like yourself to get to that ground truth and really make big strides in MS understanding in diagnosis and in treatment and, hopefully, cure.

[(5:31)] Stephanie: Yeah, absolutely. And you know, mice have been so important but making that bridge from mouse model to human model is another important gap that you're certainly filling.

[(5:42)] Dr. Riley: The animal models are limited, right? They- each, um, particular mouse model serves, I think, a purpose and can be illustrative of certain aspects of the disease, but I think we certainly have yet to find a perfect animal model.

[(6:00)] Stephanie: Yeah. So what are the research priorities of the Brain Bank right now?

[(6:04)] Dr. Riley: Essentially, we are a resource, and so, while the investigators in the Brain Bank which include myself, and then we have three principal investigators, Dr. Philip De Jager who's my colleague and my boss here at Columbia, um, Dr. Daniel Reich of the NIH, um, Translational Neuroimaging Section, um, and Dr. David Pitt at Yale who's in Neurology and also really does our histology for the Brain Bank. We all have interests, otherwise, we wouldn't be building this resource. But the real goal of the Brain Bank is to serve the community as, um, a place to come to for reliable well-characterized tissue for your own experiments, uh, for your own research projects. So, I- I really, while I'm very excited about things that I'm pursuing through the resource that we're building, I think that, um, the message that I want to send to people who might consider donating their brains or people who are interested in getting involved in research is that we're building this for the community. That's the mission that we received from the National MS Society and that really is the one that we've internalized and are- are trying to- to put forth into the world.

[(7:22)] Stephanie: Awesome. So, have you had any surprising or particularly interesting discoveries?

[(7:28)] Dr. Riley: Well, what's interesting... there are a lot of interesting things about working on this project. And in terms of sort of big reveals about pathology, there have been a few. So, right now, we're very open in terms of individuals that we're accepting as donors into the project. I'll say the eventual goal is to have every person who donates tissue through this Brain Bank be someone who we followed in life so that we know their disease state very well. But at the beginning of a project, um, we've been much more open to people who have just decided that they want to donate their brains but they haven't been followed longitudinally with us. And so, now, we're trying to get as much detailed information as we can from individuals' loved ones or from their medical records so that we can have the best characterization possible until such point as our cohort comes to maturity and fruition. So, that individuals that we enrolled and, you know, meet at a later life are now reaching the end of their lives. So, right now, we've enrolled quite a few people in that prospective cohort but the donations that are coming in are not necessarily from those individuals yet.

What I found in talking with loved ones and next of kin whose, um, family members have donated their tissue is there's a lot of misunderstanding about disease phenotypes, and many people, you know, have I think a misunderstanding of what type of MS they have at the end of their lives. Um, they think perhaps that, you know, because they had relapses early on that they'll always have relapsing-remitting MS

or any worsening of symptoms is- is truly a relapse. And so, that speaks a lot to our need for better education and communication in the field because I think a lot of people have that fundamental misunderstanding of even what a relapse is or how your disease may change over time.

In addition, we've had a few people who donated their brains and, uh, we found that they had diseases they weren't aware of. Um, so, um, metastatic cancers, for example, neurodegenerative diseases, um, and we don't know if people were really symptomatic from these or not, um, but we do find, you know, expect the unexpected in- in pathology as in life, um, and- and we're learning these things. And part of the experience of your loved one donating his or her brain to the project includes receiving a pathology report if you choose to and so we set time aside to discuss those findings with the next of kin so that they can be informed and, occasionally, that might have import to other family members or things to be aware of. So- so, we do that, uh, and that's an important part of the project as well.

One other thing is that we do that pathology report from the brain tissue, but we do often, and almost always, collect spinal cord tissue as well and there are cases where there's minimal or no brain disease, um, but a person had significantly impacted functioning from spinal cord lesions, and you know, there's a saying, right? In- in real estate, location, location, location. It's also true in neurology that the location of those lesions is so important to the impact that it will have on functioning. And so, we sometimes see people who have very low lesion burden in the brain but may have significant disability from spinal cord lesions.

[(11:00)] Stephanie: So, as a person living with MS and as a researcher, um, I obviously, like, try my best to give back to research as much as I can. So, I've never done a clinical drug trial but I've done many other research studies. I live close to the NIH, um, which is very fortunate for me and I have decided to donate my brain and NCNS tissues when that time comes. And that was a hard decision in my early 30s, but part of me is just really curious because I am one of those people who has more spinal disease than brain disease. In fact, they've never even had a new brain lesion since diagnosis. It's all been optic neuritis and spinal cord lesions, um, and as somebody who studies subtypes of MS, I'm- I'm just really curious about what- or whether my CNS tissues are going to match up to what my MRI is shown and- and the clinical picture. Um, and I feel a desire to give back to the community and, hopefully, help that next generation, um...

[(12:02)] Dr. Riley: Well, I hope we have this all solved before you have the opportunity to donate your brain, but, uh, but I thank you for your commitment to research and, um, I think it's really a wonderful thing to do. Um, a couple of responses to that, though. I mean, as we understand more about different phenotypes of MS, we also understand some things that are not MS, right? So, I'm sure you're familiar with the

MOGAD Syndrome and, um, neuromyelitis optica, and these things that I'm not that old but when I came up and came through training this was, you know, I think the first person that I took care of as a medical student who had, quote-unquote, "multiple sclerosis". They said, "Oh, she has that bad MS," you know, and it was just affecting spinal cord, uh, and optic nerve but very severely and she was, you know, a wheelchair user and, uh, legally blind, and, you know, in retrospect, she clearly had neuromyelitis optica. And so, as we carve out these other disease states, we better understand multiple sclerosis. So, might it be that we better understand it, you know, in 10, 20 years and- and say, okay, if you have optica spinal predominant disease, we call it something else, or we don't or we just recognize that certain immunotherapeutic strategies might work better for this, you know, type of- of, um, targeted inflammatory disease. It's hard to know, um, but I think that work like this when we capture the tissue and can do really deep analysis of it, um, will- will put us in the best position to answer that question.

[(13:43)] Stephanie: Absolutely. And neuroscience has come leaps and bounds even in the last decade and MS treatment has come leaps and bounds and I can only imagine where we're going to be in 10, 20 years from now. So, as you said, it's so important to start this resource now so that, in the future, when we do understand MS and understand these mimickers of MS, we have a rich resource that we can continue that, uh, legacy of research, which I think is really, really important. So, tell me, you mentioned that you collaborate with the NIH, what happens to the samples? Because I know some of it goes to the NIH, some of it comes to you, tell me a little bit about that.

[(14:18)] Dr. Riley: The samples go on a real journey. Um, so when an individual enrolls, first of all, in the prospective study, we can do that at a distance. So we have people right now, just the United States, although it's a conversation as to whether, you know, we could accept people from abroad, but right now, anywhere in the United States, we can enroll someone, um, we will do an annual telehealth visit where we assess cognitive function, we ask questions about the person's MS, treatments, symptoms, um, we can do a pretty deep assessment of their cognitive function and area that I think is extremely important and often overlooked in the disease. Um, and then once every three to five years, we'll send an activity monitor and so do two weeks of an activity tracker that will give us things like step count, but also sort of, um, some information about balance and circadian rhythms and sleep that we find very interesting and valuable. And in individuals who are nearby to us, we would also collect fluid-based, um, samples. So, usually, blood but sometimes spinal fluid if people are, um, getting one done for other purposes, we could collect that.

Um, and then, at the time, um, of death, we will arrange for removal of tissue locally and that's done through an incision in the back of the head, so everything's posterior. There's really no disfigurement. And so, whatever type of service, uh, that the family

and the individual wish to have can- can happen, and it's done within 24 hours of death. And that's to optimize the usability of the tissue and then shipped overnight on wet ice to our site. And Columbia is the hub for the Brain Bank. Um, when the sample comes in, we will divide it in half, and one hemisphere is preserved, uh, for two weeks before it's shipped to the NIH for imaging. When that hemisphere goes to the NIH, it goes into an MRI, which is a 70 scanner, a very high field scanner, and it's scanned overnight. And so, a long scan time, very, very detailed imaging. Obviously, the sample is very still which does help us get really tremendously beautiful, um, pictures of the brain.

[(16:42)] Stephanie: Yeah.

[(16:42)] Dr. Riley: And so...

[(16:43)] Stephanie: There's no way you're getting me in an overnight MRI. [laughs]

[(16:44)] Dr. Riley: Heck, no. Absolutely not, forget about it. Um, so the other half, that- that's not preserved, um, because you can do very different things with fixed tissue and frozen tissue. So, um, we will section that tissue and when the section goes through a lesion, we'll make sure to- to mirror and you'll freeze half and fix half so that you can do things like spatial transcriptomics, you know, to really understand what, um, what genes are active in these particular cells and understand on a cell basis, um, what's happening in the tissue and then match it with the fixed tissue in which you can do different types of analyses. So that's what happens with the, uh, with the fresh half. So, alternating slabs are fixed in frozen. And then on the hemisphere that comes back from NIH, our colleagues, and collaborators at NIH led by the wonderful Dr. Danny Reich, um, will actually 3D print a brain cutting box so that we can co-register those MR images with the pathology.

So, you can imagine that there's just a spatial resolution problem with having this, um, you know, beautiful, extremely detailed image, and then you try to slice the brain. Um, so using the 3D brain, uh, 3D printed brain cutting box is a great innovation for us and helps us to more accurately, um, marry the post-mortem imaging with the pathology. Um, so that comes back to us with the cutting box. And then that sectioning is done and then lesions and certain specified elements of non-lesional tissue will go to our collaborator at Yale, Dr. David Pitt, and he does a characterization of the lesions. And the part of this protocol that's still in evolution is then presenting to requesting researchers, sort of, a menu of offerings. So, we'll often get people who will request, you know, I'd like 10 samples of prefrontal cortex or something like that and that's very straightforward. We know where this is and everyone and, um, and this can be selected and- and shipped out. But people might say, "I'd like 10 chronic active lesions," or, "I would like, you know, three acutely active MS plaques.

And, you know, there are a few challenges to fulfilling those requests. One is that we don't often collect specimens of people that have very active disease. Thankfully, people are living a long time with MS and dying from usually other things. Um, and so, very uncommon to really see active MS lesions. Now, chronic active, we do see, um, so we're trying to characterize these lesions and then get to a point where we're presenting them in a way to researchers that, um, they can really get what they want to answer their scientific questions. That's still in evolution but- but we're working on some strategies and really trying to integrate the imaging, uh, which is one of the things that sets our Brain Bank apart from others.

[(20:01)] Stephanie: So, how many people do you want to enroll in the Brain Bank? And you already said anyone can participate but are there particular patient groups that you're hoping to recruit more of?

[(20:10)] Dr. Riley: We think we'll need to recruit between five and ten thousand people with MS. And, of course, it depends on the age in which we recruit people but we hope to recruit across the lifespan so that some people we'll follow for a long time and some people for not as long. Um, and then our goal has been to collect around 20 brains of MS participants, uh, as- each year. And I'll say in the last four or five years now since we've started, um, we have a total, I believe, of 62 brains. And so, these are not all from people that we had characterized in life so we have not fully realized our mission, but certainly in the last couple of years, we are hitting our target in terms of accrued brains. Um, almost everyone right now that is registered with the program has MS and we're also very much in need of individuals who don't have a neurologic disease, but maybe they care about someone who does and are willing to participate as a healthy control or anonymous control. Um, and that is an important part of our recruitment strategy that we have not focused on as much, um, yet.

In- in addition to bringing in healthy people, um, we are very interested in making sure that our Brain Bank reflects the, um, population of individuals who have multiple sclerosis. One of the enduring challenges in MS clinical research is a relative lack of diversity - racial and ethnic diversity particularly - and this is also manifest in the branch that we've collected thus far. We have a little bit of diversity but not as much as we'd like and not as much as really reflects the- the country. Um, we've enrolled people in our prospective cohort, um, now up to around 600 individuals in the prospective cohort and the demographics of those individuals really does look like the country of people who have MS. Um, so I think we're much closer to that, um, but still work to do and we really need to ramp up our enrollment and the prospective cohort so that we can be capturing, you know, the- the vision of the- of the project which is to really deeply understand what's happening with the disease of those people who will eventually donate their brains and tissues to the bank.

[(22:41)] Stephanie: So, I talked about why I chose to donate. In your experience, why are the other participants choosing to donate?

[(22:47)] Dr. Riley: I think that choosing to donate your brain is often a decision based on wanting to- to give back to society and also to make the world better often for an individual's children or other family members. I think that many of our participants want to just make the world better for other people who have MS. And one experience I've had in talking with family members of people who have donated or who are deciding to do so, so it gives them a lot of comfort at the end of life to know that their loved ones wish came true, that they were able to make, uh, a donation to the Brain Bank. Actually, it has given a lot of solace to individuals. Another thing that we do as part of our processes is give family members or next of kin the- the opportunity to tell their loved one story, and sort of their- their origin story. Um, and we do that and share that in a- in a place on our website that we call the Hero Wall. Uh, and it's been a really lovely and heartwarming part of the project for me to- to hear and read these stories, um, of our donors and how they live bravely often with MS in a- a time when the disease was very challenging, um, certainly very challenging for them and- and probably at a time when many fewer treatments were available and opportunities were available for- for people with MS. So, it's quite inspiring to me and I think, um, to- to many.

[(24:24)] Stephanie: Yeah. And I can feel us both getting a little emotional talking about it, right? And a lot of these is we're talking about Brain Banks and the heavy science, but it comes down to this deep drive to help people and to better understand this really terrible disease.

[(24:43)] Dr. Riley: Yeah. And you know, I think that every person's journey is really unique. So, oftentimes, people ask me what to do whether it's about clinical care, you know, and my work as an MS neurologist or, you know, mentees are asking me what they should do with their careers. You have to find your own path and I want people to come to this project with the confidence in the science that we're going to do good things with the tissue that's been donated, and that we have a deep respect for the individuals who are making this gift, and that we're going to, with all of our power and the might that we all have as scientists and as clinicians, really try to make the world a better place. And so, we want to be a trusted place, uh, to make this kind of donation. We really believe in the mission and in providing these resources to investigators that have ideas. Again, we're not involved in vetting those ideas. We- we make sure that tissue is going out to reputable real researchers, um, that are, you know, nobody's selling this stuff on eBay. But we otherwise are not, you know, vetting those ideas. We're really providing the tissue to qualified scientists.

[(26:09)] Stephanie: Yes, I love that you're leaving room for new innovative research to come to you and to provide again this rich resource. And as somebody with MS,

really love the stewardship and the care that you put into creating this rock-solid amazing protocol to make sure you're maximizing every cell that people donate, um, and I'm really excited to see what comes out of this because I think that the potential is limitless.

[(26:40)] Dr. Riley: And a lot of the data is also inexhaustible, right? So we acquire these high-resolution post-mortem MRIs, um, you know, we- we seek to generate additional sort of high-dimensional data from the sample. So, we're not yet funded to- to do that. But my hope is that we'll be able to, you know, really, um, develop more inexhaustible data that we can share, um, with researchers. So, obviously, the tissue is exhaustible but the images of it are not, and-

[(27:14)] Stephanie: Mm-hmm.

[(27:14)] Dr. Riley: Um, and so we'll- we'll be, you know, continuing to push forward to expand the offerings that we have at the MS, uh, at the National Brain Bank.

[(27:24)] Stephanie: Thank you so much for sharing all of that great information. How can listeners learn more about this program?

[(27:31)] Dr. Riley: You can find us on msbraindonation.org or through the National MS Society if you search for tissue donation. We are available and able to enroll people in the prospective study across the United States at this time. We're looking into options for off, uh, overseas in the future. Um, but for right now, enrolling in the project and participating as you live with MS is also a huge gift. Um, we can learn more about the disease through this process together and we are able to take on all of the work of the donation when that time comes in partnership with your next of kin or health care proxy. I'll just underscore that there's no cost associated with participating in the study. And after the donation is complete, remains are returned to the family within 24 hours and the family can proceed with burial, cremation, whatever that they have chosen, and whatever their plan is.

[(28:36)] Stephanie: Thank you, Claire, for being here and sharing all this wonderful information with us here today.

[(28:43)] Dr. Riley: It's really my pleasure. I love getting to know what you all are doing at Can Do MS and happy to be a part of spreading the good word about research and the National MS Brain Bank.

[(28:53)] Stephanie: Thank you for listening to this episode of the Can Do MS podcast. If you liked this episode, please leave us a rating and review on Apple podcasts or Spotify. We really appreciate your feedback. For more information, please visit our website at cando-ms.org, which is cando-ms.org to get additional resources and

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