Welcome to the Cutting Edge Health Podcast with Jane Rogers, where we discuss science to help prevent cognitive decline.

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[00:00:00] Jane Rogers: *Welcome to the Cutting Edge Health: Preventing Cognitive Decline* podcast, where we're making 90 the new 40. I'm Jane Rogers. Buckle up for interviews with the world's brightest minds to help you live longer, better.

Diagnosing Alzheimer's has been challenging while the patient is still alive, but some cutting-edge research happening in Boston is worth paying attention to. Our guest today is Dr. Manju Subramanian. She is studying eye-based biomarkers for Alzheimer's at the Boston Medical Center. Her goal is to look into the eye early, long before the cognitive decline starts, to detect problems in time to turn things around.

Manju, I'd like to welcome you and thank you for the time to share with us about your research.

[00:00:47] Manju Subramanian: Thank you for having me.

[00:00:48] Jane: Tell us about your life. Tell us about your research. What have you and your team just accomplished?

[00:00:54] Manju: I actually am an ophthalmologist. I went to medical school in Kansas City, Missouri. During medical school, I did some research in the area of neuroscience. I thought that I would go into neuroscience or neurology at the time, but I ended up falling in love with ophthalmology. After completing my training, I circled back in terms of my research interests to neuroscience.

This was actually a great way for me to leverage my interest in neuroscience and apply it to the eye. I've been really focused on studying the eyes' connection to the brain, particularly as it relates to neurodegenerative disorders such as Alzheimer's disease. For this particular study that you had contacted me about, we actually found a link between eye fluid. We were able to link that to the proteins in the eye fluid to confirmed pathological brain diagnoses because diseases like Alzheimer's disease and chronic traumatic encephalopathy are not actually confirmed until post-mortem examination of the brain. These are what are called clinical diagnoses that are made based on clinical presentation, but there's no confirmation until after death. We were able to connect markers in the eye fluid to pathological diagnosis in the brain.

[00:02:18] Jane: This is really exciting because you're right, we could not get a for sure clinical diagnosis until after someone had passed. What you're saying, you and your

team are able to look at the fluid of the eye, like that little film on the eye or even tears, and be able to see in there. How early are you seeing the changes of Alzheimer's? Does it have to be full-blown MCI or something before you can see it, or are you seeing things decades before?

[00:02:44] Manju: Well, that's a really good question. That question remains to be answered. Right now, the way Alzheimer's is diagnosed is, as I was saying, based on clinical findings as well as testing such as MRI and PET scan, and even taking the cerebrospinal fluid from a lumbar puncture. Fluid that supports the brain tissue and the spinal cord can be extracted and examined. That's how you can help to confirm the diagnosis in a living person.

Obviously, the holy grail really of Alzheimer's research is early diagnosis. Because the unfortunate thing about Alzheimer's disease is that pathologic changes occur in the brain, as we know, 10, to up to 20 years prior to the onset of symptoms. By the time you start therapy after symptoms develop, it's often too late to have much meaningful effect pathologically. The holy grail is really early diagnosis, and ideally to try to screen for that.

The ideal screening tool is something that's non-invasive and something that's not expensive. Obviously, we can't go around screening everybody with MRIs and we can't do lumbar punctures on everybody. The ideal screening tool is like a blood test. Where it's minimally invasive, and it's relatively inexpensive. There's a lot of research now being done on blood-based biomarkers, among other things, such as looking at photographs of the eye, the retina, through a method called optical coherence tomography that images the cell layers of the retina, which is the nerve tissue layer that lines the inside back wall of the eye. It's connected to the brain, and the retina receives the visual information we see.

There's a lot of research being done on that. Where I'm actually focusing my research is looking at proteins similar to the proteins we look at in cerebral spinal fluid. We're looking at those in the eye. I feel like that might be a more specific way to help diagnose Alzheimer's disease. I think finding the link is the first step, and then we really need to do more research to answer your questions about how soon before we develop symptoms can we detect these changes in the eye.

[00:04:57] Jane: Right now you're not quite sure how far in advance you can see those symptoms. In other words, if you're looking in someone's eye, if you're studying their tear or the fluid on the outside of their eye, can you tell in the very earliest moments, "Uh-oh, this person's headed for problems. We need to be really proactive with our prevention steps here."? How early in your research and seeing patients, how early have you been able to detect?

[00:05:17] Manju: We have been able to detect changes in live patients in the stage of…it's a continuum state. We've been able to see levels in the normal cognitive function stage and patients with mild cognitive impairment. We did find some evidence that proteins in the vitreous, specifically amyloid-beta and tau proteins, do change as patients develop cognitive changes based on mild cognitive dysfunction.

We found this in a group of patients who have eye disease. We know that patients who have eye disease tend to be an at-risk population. They represent an at-risk population for dementia. By studying this population with eye disease, we think that we can gain some insight that might be applied to the larger population. To answer your question directly, we don't really know.

[00:06:11] Jane: When you say eye disease, are you talking macular degeneration? What kind of eye disease are you seeing in these people who are more likely to develop?

[00:06:18] Manju: Patients with macular degeneration, patients with glaucoma, those are the two big ones. Then also patients who have diabetes. We know diabetes alone is a risk factor for dementia. Patients with diabetes can also develop diabetic changes in the eye called diabetic retinopathy. The three big ones are glaucoma, macular degeneration, and diabetic retinopathy. Those are the patients that we are looking at.

[00:06:44] Jane: What is that like for you as an ophthalmologist to be on the cutting edge? Having an eye appointment is an intimate experience. You're like 12 inches apart from someone. Here you're able to see into their brain by looking at their eye.

[00:06:57] Manju: It's really the only sensory that allows us to do that, where we can look into the eye and be able to visualize a nerve that connects the eye to the brain. We're able to visualize the optic nerve, we're able to visualize the retina, which contains the light receptor cells that receive the visual information we see. As they say, the eye is the window to the soul; it's also very much a window to the brain.

[00:07:21] Jane: When I am at my ophthalmologist getting my annual appointment, he checks my optic nerve back. How much more technology does he or she need in her office to do what you're doing? Is this going to come in a year? Is this just a software upgrade, and then all the ophthalmologists can really do this? Are you going to train everybody up?

[00:07:38] Manju: Right. I think if the research goes as far as suggesting that testing eye fluid can be a diagnostic tool or even a screening tool for eye disease, then that's certainly something that can potentially be applied broadly. That's the key to a screening tool. It needs to be non-invasive or minimally invasive, very inexpensive, and something that can be applied broadly. That would be down the road if all the steps in between

point in that direction. That could ultimately be something that we do, perhaps test eye fluid as a potential means to diagnose Alzheimer's disease and other types of dementia.

[00:08:17] Jane: What are the next steps for you and your team? You've discovered this, you can spot it in the eye fluid, so what are your next clinical trials going to be? To see if you can further this down the road.

[00:08:28] Manju: The next step really is to validate these findings with known markers for dementia. For example, we want to check the eye fluid levels and compare them to MRI findings in living patients. Now we know that there's a connection in the latest stage, which is, unfortunately death. We can actually examine the brain. We know that there's a strong connection there with eye fluid.

Now the question is, and to also answer your earlier question, how long preceding that are we able to detect those changes? We start by validating those results with, for example, the protein markers in the eye levels. We validate those levels with MRI findings or levels in the cerebral spinal fluid. Because right now that's the gold standard. The gold standard for diagnosis is clinical symptoms, MRI changes, and neurocognitive testing. We want to try to validate our levels in the eye with those changes in the brain that we see on MRI and cerebral spinal fluid.

[00:09:32] Jane: About how long do you think that this is going to take before you can validate all of those things?

[00:09:37] Manju: It's a good question. We all want research to happen faster than it actually does.

[00:09:42] Jane: We do.

[00:09:42] Manju: Just a question of…it may take in the order of months to several years. A lot of it just really depends on how many researchers are involved in this. That's why it's really important to not be the only one studying this. I think if we can get more people interested in looking at the eye, that's going to help the research move forward more quickly.

Right now there are a lot of people that look at ocular imaging, looking at, for example, optical coherence tomography, imaging of the retina and looking at the cell layers. That's been going on for many years. There's some really great data out there looking at that. There aren't a lot of people who are looking at eye fluid specifically as a means for diagnostic testing. The more people we can get that are interested in this research, I think, the faster the research will move forward.

[00:10:31] Jane: From a layperson's perspective, when I look into someone's eyes, like my dad passed with Alzheimer's, I looked into his eyes, he had macular degeneration-2. I could see, or maybe I was imagining it, can you see like a film? Do their eyes become less clear? Can a layperson look in someone's eyes and see anything of important?

[00:10:51] Manju: No, it's difficult. To be able to visualize macular degeneration, it really requires a dilated eye examination and a direct examination of the retina. It's not something that's really possible when you're looking directly at someone's eyes. The idea of seeing a film, sometimes that's a reflection. If he had previous cataract surgery, you can sometimes see a reflection from that. There could be other things going on with the eye that give the appearance that they may have a film to them, but not usually with macular degeneration. That's interesting that he had macular degeneration and Alzheimer's disease.

[00:11:26] Jane: It's what you are noticing in your patients as well. Are you having trouble finding patients to participate in this research?

[00:11:31] Manju: Right now we have been focusing on patients with eye disease, and one of the next steps is to try to get patients who don't necessarily have eye disease to bring them in on this research. One of the reasons why we focus on patients with eye disease is that it's much easier to obtain fluid specimens from patients who are already in the eye clinic getting clinical care, and they tend to be more receptive to it because they're already there getting their eyes taken care of. Yes, it's a good question.

Right now I haven't had a lot of challenges, but that's because we've been focused on patients with eye disease. I think if we try to expand it to a larger population, that remains to be seen. My hope is we'll be able to get enough patients that agree to participate.

[00:12:15] Jane: Tell me what motivates you. Why are you doing this?

[00:12:18] Manju: I wish I could say I have personal experience with Alzheimer's disease. I do not. I do have some family history of mild dementia, but I think neuroscience, neurology on the brain has always fascinated me, and I've always had a very keen interest in neuroscience. Yet I became an ophthalmologist, which is obviously somewhat related to neuroscience, but not directly involved with the brain. I think just being able to merge the two things that I'm passionate about, which is the eyes and the brain. This research has allowed me to do that.

[00:12:51] Jane: That's great. Tell me anything more about the research that we should know. Is there anything that we haven't touched on that you think is important?

[00:12:58] Manju: I think that we've covered a lot, particularly when it comes to the eyes' connection to the brain. I think just taking a big picture perspective, I think for patients and family members who have loved ones with Alzheimer's disease it's just that there's a lot of research going into this disorder. There's a lot of investment by the National Institute of Health, particularly the National Institute of Aging. It's a huge priority for them to fund research related to Alzheimer's disease, particularly in the area of diagnosis and therapeutics. Therapeutics, obviously, because they want to be able to treat this disorder.

Diagnosis is very, very important, particularly in as early a stage as we can possibly get it in order to start the therapeutics in order for them to have meaningful effect. I would say that for people who have loved ones with Alzheimer's disease is to just stay on top of the research. People like you, Jane, who are bringing attention to this potentially fatal disease is really, really important. I appreciate you doing that. I appreciate you inviting me to talk about this today.

[00:13:59] Jane: It was my pleasure. Thank you. I want to thank you so much for your time and for the research that you're doing. Thank you. You have a great day, okay?

[00:14:06] Manju: Okay, I will. Thank you very much. Bye-bye.

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