

Speaker 1:

Welcome to the Eye on the Cure Podcast, the podcast about winning the fight against retinal disease from the Foundation Fighting Blindness.

Ben Shaberman:

Welcome, everyone, to the Eye on the Cure Podcast. I am Ben Shaberman, Senior Director of Scientific Outreach at the Foundation Fighting Blindness. And I'm very pleased today to have with us, Dr. Nieraj Jain. He's an MD and he is an accomplished retinal specialist, a surgeon. He works in imaging as well, doing imaging of the retina using some advanced technologies. His official title is Assistant Professor of Vitreoretinal Surgery and Retinal Diseases at Emory in Atlanta. And I know Dr. Jain is going to provide us great insights into surgery, imaging, what IRD patients, inherited retinal disease patients can do to manage their conditions better. But first, before we get started, I first of all, welcome Dr. Jain, to the podcast. It's great to have you.

Dr. Nieraj Jain:

Thank you, Ben, for having me. It's a real pleasure.

Ben Shaberman:

Sure. But before we get started, I want to give our listeners a review of some of your credentials, because they're very impressive. First of all, you got your undergraduate degree in Biological and Environmental Engineering at Cornell. Then, Dr. Jain, got a medical degree at Duke. He did an internship in internal medicine at Rochester. Then he went back to Duke, for his residency in ophthalmology and there he was chief resident. And then, he went on to the University of Michigan and Casey Eye Institute in Oregon for fellowships. And I have a note here that at Casey, I believe you studied specifically inherited retinal diseases. Is that the case? Do I have that correct?

Dr. Nieraj Jain:

That's exactly right. My time at Michigan peaked my interest and I learned some there and then, did a kind of an exclusive fellowship in inherited retinal diseases with some well known names in the field. Dick Welber, Mark Pennesi, Polly [inaudible 00:02:38]. And you may or may not recall that my time there was actually funded by a grant from the Foundation Fighting Blindness.

Ben Shaberman:

Well, thank you for mentioning that. We're very pleased to help you with the career development award. So, what inspired you to get into this field? Because you started off in biological and environmental engineering. Did you know at that point that you had an interest in the eye or did you develop that interest as you went along your journey?

Dr. Nieraj Jain:

Yeah, I really didn't have a clue as an undergraduate student. When I think back to it, it was really when I was starting medical school almost 20 years ago now, at Duke. And I initially felt a little bit lost. I explored a number of fields and didn't know exactly what I was going to do, but I had my aha moment. And I still remember my first day rotating in the ophthalmology clinic, when I first had the opportunity to examine a patient's eye using the slit lamp microscope. As you may recall, if you see your eye doctor and they have you put your chin in the chin rest and they shine the bright light at your eyes, that's what

the slit lamp is. And I just remember being awestruck at looking at the iris for the first time. It's really beautiful when you look at it under high mag. And if you're curious, you can do a Google images search for a slit lamp photo of the iris, it's remarkable.

And as I examined that patient further, I appeared past the iris and I could see the retina. The retina is part of the central nervous system and I was able to visualize it with this microscope and I could see the optic nerve and the macula, the fovea, these are millimeter or sub-millimeter structures that I was examining in real time and that really clinched it for me. And then, I also recall later that day, I was heading back from the rotation with one of my best friends and I asked him, "What'd you think of that day in the ophthalmology clinic?" And without skipping a beat, he said, "I thought that was incredibly boring." And there I knew, okay, there's something going on here. This is something for me. I think I'm cut out for this field. And it kind of all went from there.

Ben Shaberman:

Well, we're really pleased you didn't find the retina a boring structure to get involved with. Was there a particular experience that put you down the inherited retinal disease path? Because that's a pretty specific path.

Dr. Nieraj Jain:

It truly is. And again, some of it is just being in the right place at the right time. When I was at Duke, I went to medical school there not knowing that they had some of the best retina specialists in the world. And then, I went for my surgical retina training at the University of Michigan, not knowing that they have one of the preeminent centers for inherited retinal diseases in the world. And so, there I had the opportunity to learn with some really gifted clinicians, including a colleague of mine in [inaudible 00:05:44] Jackson, Sandara.

And that's where I got my initial interest in inherited retinal diseases. And I've had mentors who told me, sometimes it pays off to take the road less traveled and a specialty in inherited retinal disease is certainly is the road less traveled or was, at least 10 years ago when I went down that path. Nowadays, it's actually becoming a pretty popular field for young trainees, because they see all the exciting progress and the promise for novel therapies on the horizon. But for me, at that time, it was a road less traveled and I'm very fortunate and glad that I made that. I kind of had the courage to think about my own personal interests and take that road less traveled.

Ben Shaberman:

And that's an interesting observation, because I know when I started with the foundation quite a few years ago, it seemed like inherited retinal diseases was really on the fringe. But with the advent of trials and gene therapies and other modalities, it's where the cool kids are hanging out now. So, I'm glad you anticipated that. One reason I wanted to have you on the podcast, because I've wondered about this for a long time, about what inspires one to do retinal surgery? Because when I've seen videos of it, when I think about it, it seems like something really challenging, really delicate. I just can't imagine doing a retinal surgery. So I'm curious what drew you to the actual surgery aspect of it.

Dr. Nieraj Jain:

You're right, it is challenging and delicate. And I think as a beginning trainee in ophthalmology, the first surgeries you learn include things like cataract surgery. Those are incredibly delicate and take a lot of skill on their own. As a trainee, however, sometimes you run into trouble with the cataract surgery and

you can't always get yourself out of trouble, you need to call the retina specialist. And there's something appealing about being able to address anything that might be going wrong with the eye and that's part of what drew me to retina surgery. Now, I don't want to take anything away from the cataract surgeons, those who do cataract surgery day in and day out, they do them beautifully. And again, very delicate surgery in its own right.

But certainly, being able to address any aspect of ocular pathology that's happening in the back of the eye was part of the appeal. There's also tremendous amount of innovation and the amount of technology that we use is really interesting. And I think we can all say retina surgeons and ophthalmologists love their toys because we have a lot of them. But you're right, it is delicate challenging surgery. But with the aid of these amazing technologies and surgical microscopes that enable us to visualize the retina in great detail, we are now able to do a lot of retina surgery in a very safe and efficient manner.

Ben Shaberman:

And what are the typical surgeries that you do in your practice?

Dr. Nieraj Jain:

So I'm an adult vitreoretinal retinal surgeon. And for adult surgical diseases of the retina, mostly, we're talking about things that arise in middle to late life. And so, around the age of 50 to 75 and that's when there's some physical changes happening inside the eye. The vitreous gel that fills up the eye comprised of mostly water but also, some macromolecules ionic acid and collagen. That gel structure starts to evolve and change and pull away from the retina. And during this process, we can have some complications, things like retinal detachment, macular hole formation, epiretinal membrane formation, things that can affect our vision. And so, those are the types of what we call bread and butter, surgical retina diseases that we encounter and take care of.

Ben Shaberman:

Interesting. And you mentioned that you have a lot of cool toys that you're using, especially imaging technologies to help you visualize, I presume what you're doing. Can you talk about some of those cool toys that you use?

Dr. Nieraj Jain:

Yeah, sure. So, I'll start just by talking about the imaging or the technologies that we use in the operating room and happy to talk about some more toys that we use in the clinic. The first thing is being able to see all the retina in great detail is the first hurdle in intraocular retina surgery. When we operate, we're looking through the pupil. When we dilate the pupil, maybe this is the black part in the middle of your eye as you recall. And we're talking about the maybe a seven millimeter aperture. While the retina spans much of the back wall of the eye and we want to be able to see all those details way out to the peripheral retina. And so, we have these wide angle visualization systems that we can see all of the retina in good detail, that enable us to work safely.

The second I want to highlight is the vitrectomy instrumentation. As soon as we enter the back of the eye, we're in very privileged space. We're working in the vitreous gel and the vitreous gel is connected to the retina. Any type of surgical maneuver we do in this space can transmit forces to this delicate retina. So we have to work very carefully. The vitrectomy instrumentation allows us to do that safely and it allows us to remove the gel. So we are actually removing the vitreous gel as one of the first steps of

any retina surgery. Once we get the gel safely out of the way, then we can work on the retina and address any pathologies that we may be dealing within the retina.

Ben Shaberman:

And I know a common imaging technique used on the retina, even when you're not getting a surgery is the OCT, optical coherence tomography. I've been to the retinal doctor, they have you stick your head up to that small device and they get the side view of the retina, the different layers that the OCT captures and it uses light to capture those layers. Are you using that technology when you're doing the surgery as well, in some cases?

Dr. Nieraj Jain:

It can be helpful. We're still learning about the utility of that top technology in surgery and it's not commonly used for most surgeries. But there's potential applications for example in gene therapy surgery and for example, measuring whether or not we delivered sufficient volume of drug under the retina. But you're absolutely right, this OCT technology is amazing and no retina specialist can function without it. When you see any other doctors, so for example, say you go see the dermatologist because you have some pigmented thing on the skin. The dermatologist says, "I think I know what this is, but let's just take a biopsy so we can look at the cells under a microscope to see exactly what's going on." Most medical fields, when they really want to know what's going on, they have to do a biopsy. Sometimes, it's harder than just taking a shave of skin cells.

Sometimes you have a lymph node in your lungs, they got to do bronchoscopy and access this part adjacent to your lung that could potentially have some risk. Well, as retina specialists, we're so privileged we don't have to do that. We can just put you up to this machine and have a laser scan the back of the retina and we get almost cellular level detail of the retina. In real time, it takes seconds to acquire. And so, that's one of the great advances in our field. The reason we can do it is, in order for us to see the light from the world around us, it has to get through our pupil and reach the back of the eye where the retina is. So, the structures of the eye are optically transparent. And so, we exploit that transparency with OCT technology and we shine this laser to the right back to the back of the eye. And then, it bounces back and we have a detector that can give us some detail about what's going on.

Ben Shaberman:

That's really cool stuff. So, let's move into a discussion about the inherited retinal diseases and what patients can do to just manage their condition, while they're waiting to either get into a clinical trial or for something to get FDA approved. Because I think it's challenging for a lot of patients with RP Stargardt disease, it's challenging because they know, at least in the short term, there may not be a treatment per se. But it's important for them to visit their retinal doctor on a regular basis, because there can be complications and things that you can help manage. Can you talk about those?

Dr. Nieraj Jain:

Yes, we're very excited about the prospects of these novel therapies. But, what can you do right now? First is this concept of nutrition in the eye and vitamin A being the big one. Many of our patients ask, "Should I be taking high dose vitamin A for my RP?" And they're referring to this landmark study that was conducted in Boston, starting in the '80s and published in 1993. Really a huge achievement by those investigators almost 40 years ago now, to be able to get hundreds of patients enrolled, taking high dose vitamin A to see if it would slow down progression of their RP. Their conclusions were that, they found a reduction in the rate of progression of disease as measured with an electroretinogram. And an

electroretinogram is where you have a bright flash of light or multiple flashes of light shown into the eye and then, we measure the electrical response generated by the retina. And if the retina's not working at all, you get a reduction of the electrical response.

That study was really impressive, but there are some limitations in terms of what they were able to do 30, 40 years ago and also in terms of how they interpreted the data. And so, I think we don't really know at this time, if and how much vitamin A slows down the progression of RP. The idea of the nutritional supplement to address this disease is very appealing. Vitamin A as you may know, is integral in the light sensing ability of the photoreceptor cells. Vitamin A supplementation would be a gene agnostic therapy, which is compelling. It's cheap and widely available and we all want it to work. But I don't know for sure if it has a clinically meaningful benefit. I'm not saying that it doesn't, but I don't know that the studies that we have to this date show that we have a statistically significant, clinically meaningful benefit for vitamin A, for slowing down the progression of the disease.

The other issues of course, are safety in medicine, our hippocratic oath is, first do no harm. I'm not sure that we know that it is safe in all patients to take these high doses of vitamin A. As a matter of fact, the levels they suggested in that study exceed the current FDA's recommended maximum daily intake. And there are subsets of patients where there potentially could be harm done. And so, when you're talking about this therapy that could be potentially given for a lifetime fat-soluble vitamin that can be stored in the liver. We can't discount the potential for adverse events in some patients.

Ben Shaberman:

And I'm glad that you are taking sort of a middle road with vitamin A, because I know in talking with different clinicians in our space, some are provitamin A, others are very much against it. And I think ultimately, it's up to the patient and their doctor, what they think is best for them. But what I will say, and I'm sure you'll concur, that if somebody is interested in vitamin A palmate therapy, they really need to talk to their doctor. It's something appropriate to try and there's a liver enzyme test that they should get on, I think it's at least an annual basis to make sure that it isn't having an untoward effect on the liver.

Dr. Nieraj Jain:

That's correct. And actually, Ben, when we met a couple years ago, you had mentioned the vitamin A pamphlet on the FFB website, which I hadn't been aware of at the time and I took a look at it and it's actually very nicely done. And so, I think that would be a great resource for your patients to learn a little bit more about those studies.

Ben Shaberman:

Yes, thank you for mentioning that. If people go to our website fightingblindness.org and search on vitamin A, you can come up with that pamphlet and we'd be remiss if we didn't acknowledge Dr. Eliot Berson. The late Dr. Berson, who did these studies and was very passionate about vitamin A therapy for RP and some related conditions. And, I guess, the last comment I'd like to make and have your concurrence is that vitamin A therapy is not for all IRD patients, because for people with Stargardt disease and some of the other macular conditions, it can actually be harmful.

Dr. Nieraj Jain:

That's right. There's some mouse model that initially alerted us to the potential for high doses of vitamin A to be deleterious if you have mutations in the ABCA4 gene, the gene that's associated with Stargardt

macular dystrophy. So particularly, if you have a macular dystrophy that's of unknown cause or if you know have Stargardt dystrophy, there's the potential that high doses of vitamin A could potentially be deleterious for you. So, would suggest avoiding high doses of vitamin A supplementation in those conditions.

Ben Shaberman:

Right, definitely. So I want to go back to something that you mentioned, you were talking about earlier on, not really in the context of IRDs, but you were talking about cataract surgery. And I want to come back to that, because for people with inherited retinal diseases, cataracts often occur fairly early in their lives. Unlike those of us without retinal diseases, they occur when we get older. What are the special considerations you or other surgeons have to take into account when thinking about removing a cataract of let's say, an RP patient?

Dr. Nieraj Jain:

Yes, so I'm glad you asked this because this issue does arise commonly in our RP patients. So just as refresher, a cataract is an opacification of the naturally occurring, the lens that we're born with. When we're born, this lens which sits near the front of the eye is crystal clear. And as we age, it just becomes a little cloudy. That process can happen a little bit faster in RP. When we have cataract, it can cause blurry vision but also can cause symptoms such as glare. For example, you're out in the car at night and the oncoming traffic is becomes problematic or even in some cases, unbearable because those headlights are bright and causing quite a bit of glare. And those symptoms are things that you want to kind of be attuned to, because they can help differentiate whether or not your symptoms are from RP or an underlying retina problem, or if they may be from the cataract itself.

In many cases, our patients with RP and cataract can really benefit from cataract extraction. But the postoperative, of course, in RP patients is a little unique and these patients don't always respond the way we anticipate they may respond. And so, I do think that if you are considering this surgery, you do want to have your inherited retinal disease specialist involved in that decision making. I think that I generally will set the bar a little higher for my patients with inherited retinal diseases. I want to see that cataract be very clearly problematic for their daily functioning before we send them over for cataract surgery. Sometimes, there can be some complications such as the lens implant that's put in at the end of surgery doesn't sit where it ought to stay and potentially could dislocate, for example.

Sometimes, it seems that maybe the underlying retina condition may deteriorate a little bit after cataract surgery and we don't really understand that process. And then, many of my patients will say, "Oh boy, I see great much better after cataract surgery and maybe I should have done it a little sooner." So, it is a very difficult decision making process that needs to involve the input of you, the patient, first of all, but also, the cataract surgeon and the inherited retinal disease specialist.

Ben Shaberman:

Thanks for sharing those insights and observations. As you said, it's a common thing that comes up for retinal disease patients. And as you're also saying though, it's something that you just can't take very lightly. It requires a lot of thought and discussion with your retinal doctor and potentially your cataract surgeon as well. So you can minimize whatever risk might be involved. So one more thing I wanted to talk about. I understand you are an investigator on a clinical trial that's just launching. It's a phase three clinical trial for a gene therapy being developed by our partner MeiraGTx Janssen. It's for people with mutations and RPGR, which causes excellent RP. And we're excited because it's going into this pivotal

phase. If this phase goes well, then potentially, the company could seek FDA approval. Can you talk more about this gene therapy and your role in the trial?

Dr. Nieraj Jain:

Yeah. So, here at Emory, we run a number of clinical trials for different inherited retinal diseases. And in this case, we are one of a number of sites around the world that is enrolling participants. I'm the principal investigator for our site here are participating in this study, first of all, because we believe in its potential. And that's one of the first questions we ask ourselves, if we want to participate in a clinical trial. Here, we'll be enrolling some of our own subjects as well as patients from around the region. Atlanta is a very accessible city to participate in these studies. So, patients from throughout the southeast have already contacted us to potentially participate in this study. If a patient has the gene mutation and meets the other eligibility criteria to participate, then we would dose them with this, but potentially enroll them and dose them with this gene therapy product.

This involves vitrectomy surgery, again, you recall. We go in the eye, remove the vitreous cell, and then, we just inject the vector underneath the retina. We use a tiny little needle with 38 or 41 gauge needle to inject little balls of fluid under the retina to get this vector to the photoreceptors. And then, we follow them for initially a year. And then, we have an extension study where patients will be followed for four years. And we do a lot of assessments of the patient to see whether or not this therapy is working. This involves doing images of the retina, including this technology. We mentioned OCT technology to look at the structure of the retina. And we do a lot of functional assessments of the retina as well to see whether or not the patient's peripheral visual field has improved or if we slowed down the loss of peripheral vision.

We do this mobility test of multi-luminance mobility test where patients walk through a dimly lit maze to see how their eyes are able to help them navigate that maze. And eventually, after some time, this data will be aggregated and analyzed across all the sites to see whether or not this is a safe and effective therapy. As you can tell, we've gotten really good at assessing retina structure and function over the decades since those initial vitamin A studies from three, four decades ago. And it does involve a lot of work on the part of the patients and our study coordinators. When patients come back for their study visits, they're going through a real battery of tests. Because we really want to investigate the retina in great detail, so we can be sure whether or not this therapy is working. And so, patients embarking on these journeys, it's an exciting prospect, but be aware that it does require patients and quite a bit of dedication on the part of our subjects that are enrolling in these studies.

Ben Shaberman:

Right. Thanks for underscoring the commitment for people who want to be in a clinical trial and people need to understand, it's still research. Obviously, there's the hope that the treatment will work and moving into phase three, that hope expands a little bit, but it's still research. There's risk, but we're excited about the potential, gene therapy has come a long way over the last decade or so since that first trial at Children's Hospital of Philadelphia, back in really 2000, late 2007 for what would become luck's turner. So we've come a long way. We still have a way to go, but the work you're doing is very exciting. And I want to remind our listeners that if they're interested in clinical trials, they can go to clinicaltrials.gov. For this particular trial, they can search on the top search bar for X-linked retinitis pigmentosa and they'll get the MeiraGTx trials. They'll learn about some other trials as well.

But really, for anybody with a retinal disease, you can search for all the trials that are underway in the US and many of the trials that are underway in other countries using clinicaltrials.gov. So, I also want to remind our listeners that if you have a question, a follow up question, you can email us at

podcast@fightingblindness.org. Again, that's podcast@fightingblindness.org. Dr. Jain, this has been a really interesting in depth discussion about the retina, the procedures you do, considerations for IRD patients, so much great information. I really appreciate you taking time to give us all of your insights and knowledge. It's been great.

Dr. Nieraj Jain:

Thank you so much, Ben, for having me. I think this is such great resources for us and the patients. I think that this field is really exploding, but it takes minds from different areas of expertise to really make this happen. And you've done a terrific job of kind of connecting the basic scientists, the translational researchers, and the clinicians, and helping distill knowledge from those different sources in a way that we can all understand better. And it's such a great resource and really appreciate the opportunity to join you on this podcast.

Ben Shaberman:

Well, it's always fun for me, I always learn. In this case, it's great to be the messenger. So thank you for letting me convey the information. So, Dr. Jain, good luck moving forward with your gene therapy trial and all your other work. And listeners, thank you again for joining us for this episode. We look forward to seeing you at the next Eye on the Cure Podcast episode. Take care.

Dr. Nieraj Jain:

Thank you, Ben.

Speaker 1:

This has been Eye on the Cure. To help us win the fight, please donate at foundationfightingblindness.org.