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'm your host Ben Shaberman with the Foundation Fighting Blindness. And my guest for this episode is Dr. Omar Mahroo, who's one of the world's foremost experts in electrophysiological testing for the retina. And just so our listeners know, electrophysiological testing of the retina is basically evaluating how retinas electrically respond to light. And that's really getting at the primary function of the retina. And I know many of you with an inherited retinal disease out there has had an electroretinogram, an ERG, and that's, I think, the most common electrophysiological test for the retina. And they aren't exactly the most beloved form of testing. So Omar, isn't that a great segue? I'm introducing you as the guy who administers a test that nobody likes.

Dr. Omar Mahroo:

That's a great introduction. Thanks. First, I just want to say it's an honor to be here. I've seen the list of people you've had on the podcast before and they really are world experts. So sorry if it's going to go downhill today.

Ben Shaberman:

Well, we're going to try to make it go uphill as much as possible. These tests are really important and I'm really excited to have you on the program so you can explain why they're important, what they do and why they're important. And just quickly, where are you based?

Dr. Omar Mahroo:

So I'm based at Moorfields Eye Hospital in London. It's the oldest and largest eye hospital in the UK and I also do clinics at St. Thomas's Hospital in London, which is just across from the Houses of Parliament. It's where I'm sitting right now, which also has a big eye department. And interestingly was the place that a lens was first placed in the eye for cataract surgery. That's a claim to fame for St. Thomas's Hospital.

Ben Shaberman:

Interesting. Well, thanks for sharing that. And you are a consultant ophthalmologist and retinal specialist and you're also a Professor of Retinal Neuroscience at University College London. A little more on Omar. He completed his medical degree and PhD at the University of Cambridge and during his undergraduate years, he achieved a triple first class status. And I want to get to that in a moment. He was named Rising Star of the Year by the UK-based Macular Society, that was in 2019, and received awards for teaching excellence and for patient and public engagement from the University College of London and the Moorfields Biomedical Research Center. That happened in 2020. He's co-authored over 130 publications. And he spends much of his time seeing patients mainly with inherited retinal diseases. He conducts research to better understand these diseases and he teaches both locally and internationally. So back to this triple first class status you received while you were pursuing your undergraduate degree, not just first class, not just double first class, but triple first class. Omar, it sounds like you get a really good seat on an airplane.

Dr. Omar Mahroo:

That's right. So the first few years of the Cambridge medical degree are basic science years and you get a grade at the end of each year. And so I was lucky enough to get a first class each of those three years. So people call it a triple first class if you get that.

Ben Shaberman:

Okay. Well, thanks for explaining that and I'm honored to have somebody with triple first class status on the podcast. So let's start off.

Dr. Omar Mahroo:

And still travel by economy, I should say.

Ben Shaberman:

So let's start off with the basic definition of electrophysiology and what are some of the tests that fall under that umbrella?

Dr. Omar Mahroo:

So exactly as you said, electrophysiology deals with detecting the electrical signals from the retina or part of the brain, the visual cortex that deals with vision. And one of the main tests, as you said, is the ERG, the electroretinogram. So just with electrodes around the eye, we deliver flashes of light or flickering light and we record the response of the retina to that light. And it's amazing that without having to take someone's eye out, just with some electrodes around the eye, you can get the responses of the very neurons in the eye to light and all of the processing that's happening in the retina. We have over 100 million photoreceptors that detect light and they signal to other cells and then to one and a half million ganglion cells that connect to the brain. And there's a huge amount of processing that goes on so that the ganglion cells aren't just signaling light and dark, but all kinds of aspects of vision like direction of movement and contrast.

And so some of that can be captured with the electroretinogram, some of those responses photoreceptors bipolar cells. There's another test called the electroretinogram, not so useful as it used to be, but that's helpful in diagnosing Best disease. And there's another type of recording visual evoked potentials, which are from electrodes that are stuck on the back of the head, right over the visual cortex, which is the main bit of the brain that deals with vision. And by putting these tests together, we can get an idea of if the retina and the visual pathway, the optic nerve and the parts of the brain that deal with vision are working properly, even though we now have really good imaging tests to look at the retina in cross-section in our patients so that in the old days we just look with a lens at the back of the eye.

And nowadays, we still do that because ophthalmologists, right, the patient wouldn't believe they'd seen an eye doctor if we didn't try and look at the back of their eye with a lens. But we get a lot more from the imaging. But still electrophysiology is important, because sometimes the imaging can look normal, but the retina is still not working properly. So the electroretinogram say if it's a retinal disease, will tell us whether the retina is working well or not and maybe even which parts of the retina which layers aren't working properly.

Ben Shaberman:

So it's really an important diagnostic tool. So you can tell which cells in the retina are or aren't working properly. Is that correct? You kind of just said that.

Dr. Omar Mahroo:

Yeah, exactly right. So I meant that in the past it was really important, because we just have lenses to look in and sometimes the retina would look normal and the ERG would tell us it wasn't working properly. With imaging, maybe the need has evolved. So not everyone needs an ERG or not as many people as before. But still even with our amazing imaging, which looks very pretty, the retina may still not be working properly. Often, so the retina's not just there to sit and look pretty on imaging, it's there to generate electrical signals and it's electrophysiology that allows us to quantitatively, objectively monitor those signals and help with the diagnosis. And we've had many patients where sometimes it's not clear what their genetic diagnosis is. You do the genetic testing and still you kind of none the wiser, you get a whole load of genetic data back and you don't know what's relevant and what isn't, or you get a negative test result and you don't know which genes really to look at in more detail.

And in many of our patients, the electrophysiology has helped guide us work out which gene or which type of variant in which genes are likely to be important in our patients.

Ben Shaberman:

And when somebody gets this test, you're putting the electrodes on their eye or around their eye.

Dr. Omar Mahroo:

Yeah, there are different ways of doing it. Basically, something you need to have electrodes kind of either side of the eye front and back obviously. How do you get it behind the eye? We just put it on the temple, so a skin electrode on the temple. And the one at the front of the eye, there are sometimes contact lens electrodes or there can be a little thread, we call it the DTL, it's like a conductive fiber that just gets placed behind the lower eyelid. And then we're measuring the voltage between those two electrodes. And we normally put another ground electrode on the forehead. If people find it difficult to have an electrode in the eye, that little thread, which is very comfortable, I've had it in my eye for hours and hours, but we can also just place an electrode on the skin on the lower eyelids rather than having to put one in the eye. And that gives you a lower amplitude response, but you can still tell quite a lot even from those recordings.

Ben Shaberman:

My understanding is that before somebody gets an ERG, they're put in darkness for a while. Is that true? They're dark adapted as you say.

Dr. Omar Mahroo:

That's right. So one thing about the retina is it can adapt amazingly to a billion-fold change in light intensities. We don't notice it, but we go out in different light environments and we don't really notice that we're adapting. It's anyone, you put an iPhone camera up and you realize why can't I see this part of the picture? Not that part. And we realize that our retinas are better than any iPhone camera, but what that means is it's very dependent. The size of the signals you record are really dependent on whether the patient's been in the light or in the dark. And it can vary a lot. It's not like say an OCT where if the patient's just been in the dark and the light, it's not very different, but the size of the signals we record can change a lot. So for that reason, tests are standardized and patients are put in the dark for 20 minutes so that we know that their rod photoreceptors are at their maximum sensitivity, and then we deliver flashes of light and record those responses and then they put in the light for 10 minutes.

So then we know the rods are saturated and we're recording from the comb system. So because of this, it's good, because it's standardized tests and there's something called the International Society for the

Clinical Electrophysiology Vision ISCEV, that set these standards before everyone was just doing different things and no one could compare. But the problem is it means that the tests take a long time. So instead of being a five-minute test like an OCT, it might take an hour or more to get proper ERGs done. And I think as well as improving the quality of testing, it has made it less accessible. You might have the Best test, but it takes 10 hours to do who's going to do it.

And part of my research and my area of activity is trying to see if we can shorten those tests and maybe some things you don't need to put the patient in the dark for 20 minutes, you just want to see some aspect of the cone system. And then you could get that information in say, five minutes with a portable ERG machine in clinic, which is one thing I'm trialing to see how that can help.

Ben Shaberman:

That's great. I think a lot of people are glad to hear that you can make the test a little shorter and perhaps a little more pleasant for the typical patient. And these tests have evolved quite a bit over the years, haven't they, the ERGs?

Dr. Omar Mahroo:

Yeah, that's right. So one big advance was just setting standards. So over in the past, people were doing all sort have different kind of stimuli and getting different recordings and you couldn't compare. And then ISCEV, this body started to set standards that are regularly updated and that's made testing a lot more uniform. One thing that brought that home for me was I was sent as a resident to Tanzania. There was a link between Tanzania and St. Thomas's Hospital and they'd been donated an ERG machine from a Japanese eye department. And I got sent there about ERGs, you go set it up. And I did go there and I looked at the manual and it was in Japanese from a Japanese eye department. So suddenly I'm there blown all the way there from London and I can't read this manual, but the ISCEV numbers were all there and so I could work out what it was doing and it was just delivering an ISCEV standard ERG.

We got it working and I felt, well, it's good that we've got a universal standard for that in that same trip then they'd made some discoveries on retinal imaging in an optic neuropathy that were really interesting. And these microcystic changes in the retina that had only been described really in multiple sclerosis before. So we helped them get that published in quite a high impact journal. And so that helped us understand that these microcystic changes seen in lots of different diseases. So I went there to do ERGs and came back with something completely different, but we got the machine working and that's because the ISCEV stimuli were there. And then with time the standards are updated, new things are added. And I think one big, but I have to say probably hasn't advanced as much as imaging has, and again, a big area of my research and others is trying to advance these tests more rather than just delivering a standard stimulus and looking at the amplitude or the timing of the response.

There's a lot more we can get from those waveforms. So a lot of my time is spent applying mathematical models to the waveforms to try and understand what's going on in the photoreceptors in the retina. And we've discovered quite a few new things with that approach. When I tell people I work in modeling, they do look at me a bit funny, "And what modeling do you do?" "A mathematical modeling of electrophysiology?" And they're, "Oh yeah, you look like the kind of guy who do that, not the other kind of modeling." Part of the evolution of tests is we're analyzing things, not just amplitudes and peak times, but we're analyzing different things that we can get from mathematically modeling the waveforms. And we also, we deliver different tests.

So the standard tests are sort of white flashes on a white background, but one thing I and others are looking at is using different colors of stimuli with clever sort of timing intervals between them to try and tease out different responses from different retinal cell populations so that we can really understand

what's going on in some of these diseases and hopefully more understanding will open avenues for treatment in the future.

Ben Shaberman:

That's great. There's another test that I've been hearing a lot more about lately and it's being used in clinical trials and I think a lot of investigators in our world hope to even use it as an endpoint for a clinical trial, a primary or secondary endpoint. And that's called full-field sensitivity or FST. And would you say first of all that that is electrophysiological and can you talk about what that test is?

Dr. Omar Mahroo:

So FST full-field stimulus testing, it's funny, everyone gives it a different definition. Some people say full-field scotopic testing, but I think it was originally when it was described full-field stimulus testing. We'd call it a psychophysical test rather than electrophysiological test. They're both big words, but electrophysiology is when you're directly recording the electrical signals. But psychophysics is when you're asking the patient basically what do you see? Do you see this or not? And so it's a psychophysical test where the patient tells you by pressing a button basically whether they're detecting a stimulus or not. And there's a big history of psychophysical testing, but one thing that was kind of advance in terms of FST was it was very simple, it's just a full-field stimulus. You're not stimulating just one tiny bit of retina and patient has to concentrate and this is the patient still has to concentrate, but this is a full-field stimulus. It's like a flash that's stimulating the whole of the retina. And in different light intensities you can work out what that patient's threshold is.

And as you say, it was an outcome measure in many of the pivotal trials and showed that patients say who'd had lux sterner, their suddenly their sensitivity was a lot higher, meaning they could detect light at much lower levels than before they had the treatment say. So it's in principle a kind of easy test still it's a bit demanding for the patient, but it has taken off as you say, because it does seem to show a change in some of these trials where are traditional measure of visual acuity, which is the traditional way we measure visual function. That doesn't necessarily improve with some of these treatments, but other things can improve like the sensitivity in the dark and that can make a big difference to a patient's quality of life, and you can't always capture that with a visual acuity. I have to say I don't do much of that, because my main area of research is electrophysiology and then just seeing patients clinically in our clinics. So I don't do a lot of it, but certainly for the trials that are going on, it is being used as an outcome measure.

Ben Shaberman:

And with FST, again, the important point you're making is you're not recording anything other than the patients acknowledging that they see the flash.

Dr. Omar Mahroo:

That's right, yeah.

Ben Shaberman:

Do they hit a button?

Dr. Omar Mahroo:

Yeah, yeah. Or some other way of saying that, "Yes, I've seen it." Whereas with electrophysiology, the patient kind of doesn't have to do anything or they've got to look straight ahead and then everything else is kind of objective. You're just recording the responses that are being generated from the retina or from the visual cortex. And so in that sense it's more objective, maybe less demanding on the patient, but for good reason FST developed, because sometimes electrophysiology wasn't sensitive at that very low light levels, especially when you're just improving a little bit of the retina, maybe not enough to show a change on the ERG. So again, another area of my research is trying to get some electrophysiology tests that we really focus on small areas of retina or you can look at a bit of retina under say fundus imaging, say I want to stimulate that bit of retina and see what response comes from it. It's challenging, because a very small response, but I think it's something that could be doable.

Ben Shaberman:

And so you do a lot of different things, Omar, you are doing research and you see patients, right?

Dr. Omar Mahroo:

Yeah.

Ben Shaberman:

You're well, you're a medical doctor and you teach as well. What do you teach?

Dr. Omar Mahroo:

Again, I teach in different capacities. Sometimes we have medical students, residents, fellows in clinic and I supervise them or teach them aspects of ophthalmology or inherited retinal disease. I used to teach as part of the M.Sc. course, there's a Master's course in ophthalmology at University College London. I've just given that up. But I used to lead the retinal module for several years. Another thing I do, which I think I find really, although it's time-consuming, it's really fulfilling, is that we do a one and a half hour every week on Monday evenings, UK time on Zoom where we just discuss retinal cases and people now that started off as we call it [inaudible 00:18:22] teaching. It started with Alan Bird many, many years ago, 50 years ago, it was in-person and it was in-person until COVID.

And then we took it online and then suddenly realized that now people can attend from all over the world, not just Moorfields. So we have people logging in from North America, from India, from Australia at some crazy time and we go through retinal cases and it's a real, really good teaching opportunity and learning I learn as well as teacher. And I guess that's another bit of teaching that I do every week.

Ben Shaberman:

That sounds like fun. I would like to attend that even though I'm not-

Dr. Omar Mahroo:

You're very welcome to.

Ben Shaberman:

... a doctor. I think it would be interesting to hear all the different cases. During your average week or month or whatever, what is your favorite thing to do? What gives you the most satisfaction?

Dr. Omar Mahroo:

So again, I'm going to give a rambling answer that's not just one thing. So one thing I appreciate about my job is it is very varied, as you said, and I feel like I never get bored, because it's a little bit of everything. So caring for patients in clinic is a big thing for me. And when you feel you can make a difference for your patients, getting the diagnosis right, that's a huge thing. It's also frustrating that for many of our patients there's no treatment, but that kind of stimulates the research side of things. And probably from that clinically, one thing I get maybe most satisfaction from is getting a diagnosis that has maybe eluded many others. So I often get sent cases or images of the retina or patient histories for opinions from other parts of the UK or other parts of the world.

And to be honest, most of the time I can't add anything, because they've been seen by really good doctors and there's not much to add. And I guess they feel reassured that I've got nothing else that they've missed. But occasionally I do say, "No, it's this," and maybe check or whatever, and then we get the diagnosis. So that is quite satisfying occasionally, because something that people think it's an IRD and it turns out to be something treatable and that's a great thing, because you can be vitamin A deficiency or something, which we don't see that much of, but we do see even in the western world times and that can be treated and vision restored. So that's one side of things.

Other things, I enjoy the research making discoveries being the person who's discovered something that no one ever knew before, and then you can communicate those discoveries and especially if we understand more about these conditions, that might then lead to new avenues of treatment. And then the other thing as we alluded to is the teaching. I think seeing people develop people either supervised as scientists or as clinicians and then they go on to do great things or develop great competence and skill as a clinician or a scientist, then that's really satisfying as well.

Ben Shaberman:

That's great. It's great to hear you express such passion for what you do and you have a lot of curiosity, and I think that's really important to your role so much for the obvious. But what actually inspired you to go down the electrophysiology route? I mean, there are a lot of ways you could go not just in ophthalmology, but in retina and you chose to study electrophysiology.

Dr. Omar Mahroo:

You are right. It's like the most obscure thing. And I'm paraphrasing someone else who is into psychophysics. He says that if he ever wanted to get rid of someone who's talking to him at a dinner party, he'd say, "I work in visual psychophysics." And immediately the guy, "I think visual psychophysics is interesting, but it's electrophysiology that really turns people off." I think if I say, "Yeah, I work at electrophysiology," you immediately see the glazed look and suddenly they've got to go or wash their hair or something. So it is pretty obscure, that's true. My route was during medical school, I found vision really interesting, so I gravitated towards the eye. I thought the way the retina works is just mind-blowing. It's like a bit of the brain at the back of the eye and the stuff that happens is so cool. And in my third year as a medical student, you could do a research project and I was inspired by a guy called Trevor Lamb, he's a scientist, now retired, who's a world expert in photoreceptors. And he was looking at photoreceptor adaptation and using the ERG.

And so I did a project with him and it was great, and we've discovered something new. We even published a paper and then I went on to do a PhD at the MB PhD program and we discovered lots more. That was new. I met Tony Moore at that time who was at that time based in Cambridge, later moved to London, then to San Francisco. And I found him very inspiring. So that kind of got me into vision and ophthalmology. And then within ophthalmology, because I had this electrophysiology background already, I kind of gravitated towards retina and inherited retinal disease. And at the same time as my

clinical training thinking, "Well, where could the electrophysiology fit in here? Where could it be useful?"

And I guess that's the thing I sort of bring to the table is that basic science knowledge of retinal electrophysiology and retinal neuroscience and then applying it to our patients rather than just standard clinical tests, thinking about how we can take electrophysiology forward, make it more accessible, make it tell us more than it's already telling us. That was early on in medical school that got me into electrophysiology. And then as I went through training, saw there's a gap there really. We've got really good imaging, but the electrophysiology takes hours and it's a visit to another hospital often or another day, and there's got to be something better we can do with these tests to understand retinal function in health and disease and hopefully do better things for our patients.

Ben Shaberman:

Thanks for telling us about your journey into electrophysiology, and we're glad you chose this road less traveled, because we need folks like you who are interested in it, because it is a very valuable resource for evaluating the retina. So when you're not flashing lights in people's eyes, what do you do for fun?

Dr. Omar Mahroo:

Who says that isn't fun, right? So I mean, I think work takes up a lot of my life, maybe I find it so kind of fulfilling, but otherwise, time with family I think is a big thing. And I do feel when my kids were small, they probably, I inadvertently neglected them quite a bit with all this focus on the clinical training and research. And so time with family, I really value and I try and adjust my schedule so that I can spend maximum time with them as they get older.

Ben Shaberman:

Well, we don't want to take you too far from your family, but we really appreciate your commitment to electrophysiology and caring for patients and just trying to get a better handle on inherited retinal diseases so we can move the research forward. Thank you for taking time to tell us more about ERGs. It was fun to go down that path and learn about something that doesn't get talked about very often, at least with patients and families as an audience. So thanks for explaining that world to us.

Dr. Omar Mahroo:

Thanks very much. It was a pleasure and an honor. Thanks.

Ben Shaberman:

Thank you listeners as always for joining Eye on the Cure. It's great to have you and we look forward to having you back for our next episode. See you later.

Speaker 1:

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