



Episode 31: Dr. Marc Gotkine - ALS and When Can We Really Expect A Cure?

Benyamin Cohen:

This is “Hadassah On Call: New Frontiers in Medicine.” I’m your host, Benyamin Cohen. In each episode of this podcast we’ll get an inside look at what goes on behind the scenes at one of Israel’s premier medical centers. We’ll travel to Jerusalem to meet up with the doctors and nurses at Hadassah Medical Organization. From striving for peace through medicine to performing surgeries with robots, they’re working on medical breakthroughs that are impacting people around the world. That’s what Hadassah is all about, the power to heal our world together. From cornea transplants to developments in pediatric oncology, we’ll learn about the latest cutting-edge research coming out of Hadassah Hospital. All that plus the inspiring stories of patients who have recovered from near-death experiences. Our appointment starts now. This is Hadassah On Call.

Benyamin Cohen:

Today’s guest is Dr. Marc Gotkine. He’s a neurologist whose specialty is ALS, also known as Lou Gehrig’s disease. He’s the head of the ALS clinic at Hadassah Hospital, where he’s conducting the latest research using everything from STEM cells to gene therapy. I met up with him a few months back when traveling was still allowed before the global pandemic, and we had a fascinating conversation, which I think you’re really going to enjoy. So without further ado, here’s Dr. Marc Gotkine.

Benyamin Cohen:

Hello everybody, and welcome to today’s show. We are at Hadassah Hospital Ein Kerem here in Jerusalem, and today we are joined by my cohost, Barbara Sofer.

Barbara Sofer:

Welcome to Jerusalem, everybody. It’s so great to be able to talk to you directly from the holy city.

Benyamin Cohen:

And our special guest today is Dr. Marc Gotkine, who works here at Hadassah Hospital. Welcome to the show.

Marc Gotkine:

Well, thank you, and thanks for having me.

Benyamin Cohen:

I can tell, I think, by your accent that you're not a native Israeli speaker. Am I correct?

Marc Gotkine:

That would be correct, yeah. I was born in the UK, in London, and actually went to medical school in London and came here just after what we call house jobs, and did my residency in neurology here and I've been here ever since.

Benyamin Cohen:

And did you know growing up that you wanted to be a doctor?

Marc Gotkine:

Sure. Yeah, I think from the age of 13, 14 it was already my plan. And as things got closer it became more clear.

Benyamin Cohen:

So your specialty is neurology, is that correct?

Marc Gotkine:

Yeah, that's right.

Benyamin Cohen:

And even more specifically, you deal with ALS, Lou Gehrig's disease?

Marc Gotkine:

That's right. So my research area is Lou Gehrig's disease or ALS, or what we call motor neuron disease in the UK. But in general I'm in the field of neuromuscular neurology and in charge of the neuromuscular activity within Hadassah.

Benyamin Cohen:

Was there a reason you wanted to focus on that as opposed to being a podiatrist or something else?

Marc Gotkine:

Specifically neurology and specifically researching ALS is mainly because of the challenge. I think that the need, certainly when I got into the field, to find treatments and in order to understand ALS, it was one of the biggest challenges. We understand a lot more now than we did when I decided to go into the field. But certainly when I was in medical school ALS was a huge mystery and we were very, very far away

from any kind of treatment. And I think it was a very exciting and challenging area that had a big unmet need. So that was the main reason.

Benyamin Cohen:

A few years ago, many people may remember that the ice bucket challenge became viral worldwide and brought a lot of much needed attention to ALS. What did you think about that?

Marc Gotkine:

I thought it was great. Anything that can firstly increase the awareness that ALS exists and that it's an important area to research, that there's a big unmet need for ALS treatments, I think just raising awareness was great. And of course all the research money that was generated, most of it went to the ALS Association in the US, but some of it did trickle down to the Israeli ALS Association. But that extra research money has done a lot. So I think it was great.

Benyamin Cohen:

Does ALS affect men and women at the same rate?

Marc Gotkine:

So men have a higher chance.

Benyamin Cohen:

Really?

Marc Gotkine:

Men are more effected. Yeah, so we don't understand the reasons why, but definitely there is somewhat more men than women.

Benyamin Cohen:

So ALS, for people who are not aware exactly, what is it, and what happens to a person when they get ALS?

Marc Gotkine:

So ALS stands for amyotrophic lateral sclerosis, and that name comes historically from a description of the fact that we have two types of neurons, or nerve cells, that die during this disease, both of which are involved in the direct control of our muscles. Some of these neurons or nerve cells are starting in the brain and they're called the upper motor neurons. And the others come mainly from the spinal cord and some from the brain stem, and they're called the lower motor neurons. And they're the ones that directly activate muscles. And in ALS we have degeneration or death of both of these types of nerve cells, which will cause someone to gradually lose control of all their voluntary muscles.

Benyamin Cohen:

So they wouldn't be able to walk, they wouldn't have much motor function?

Marc Gotkine:

Exactly. So it will affect the leg muscles and that will affect walking, the arm muscles and so you'll lose strength in your arm. But also the muscles that we need to talk and to swallow and even to breathe. And when the breathing gets affected you either need to have help with ventilation, or unfortunately the person suffering from ALS will die from respiratory problems.

Benjamin Cohen:

And is it an autoimmune disease like MS?

Marc Gotkine:

Although there is some evidence that immune functions are important, it's definitely not considered an autoimmune disease in the classical sense. So multiple sclerosis is much more of an autoimmune disease than ALS, although there could be some kind of role of the immune system within ALS. But giving medications such as steroids, which can decrease inflammation and decrease autoimmunity, which work very well in an attack of MS, they actually don't help at all in ALS. So there are very big differences. Autoimmune diseases are much more amenable to treatment, whereas ALS unfortunately is not.

Barbara Sofer:

Well, let's say when I was growing up, so one knew who Lou Gehrig was. Today I don't think it's that informative for the young people who don't know who Lou Gehrig is when we say it's Lou Gehrig's disease. And it wasn't that common, at least one didn't hear of it that often. Why do we hear so much of ALS? How common is it, and is it more common than it used to be?

Marc Gotkine:

Well, I think it's quite difficult to know how common it used to be because the records are incomplete. And I think that today we're much better at diagnosing it than we were in the past. And it could very well be that somebody was going to their family doctor and they were just told that they had something that's incurable without having a specific diagnosis. They might not have even got to a specialized center. But nowadays, now that people are much more aware of the existence of ALS and the diagnostics have improved, I think that we're picking up most of the cases, whereas we might not have been doing that in the past. Because now there are actually more treatments available and much more hope, and there's much more value in actually getting a diagnosis and being referred to the appropriate specialist center.

Barbara Sofer:

Are there treatments?

Marc Gotkine:

So there are treatments that are slowing down the disease. There's one very old treatment called Riluzole, which has an effect to slow down the disease. More recently there's a Japanese drug that was approved by the FDA called Edaravone, and it's given intravenously, that also seems to slow down the disease. But I think more exciting is the treatments that are on the horizon. I'm specifically excited for the genetic therapies, and one of the main focuses of my research is the genetics of ALS. There are two major genes that have been found to cause ALS, what we call dominant genes, which means that you only need one copy of these genes to cause the disease. And these genes are actually toxic. In other words, they're creating a protein which is actually doing the damage, and technologies are now available where you can block the expression of these genes.

Marc Gotkine:

So although someone might have the gene, you can give a medication that will actually stop the gene creating the protein that can be toxic. Now, these therapies, if you have the gene, are very, very promising. And I know that there are clinical trials in humans that are going on right now that seem to be going definitely in the right direction. But I think the main message here is how important it is to do the basic research to find the new genes that haven't been discovered yet, to discover genes that are causing ALS. And then I foresee that within hopefully the next 10, 20 years anyone who gets the disease will be able to, well, hopefully most of them, identify some kind of genetic factor that might be amenable to treatment.

Barbara Sofer:

What's your role in that and Hadassah's role in that research?

Marc Gotkine:

So actually we are very heavily invested in that project. We're part of a few different research groups. I have a very close research collaboration with the lab of Professor Chris Shaw with Bradley Smith in King's College London in the Maurice Wohl Institute in Kings, where actually I trained. So it's nice to collaborate with them because Chris Shaw and also Ammar Al-Chalabi, they were my teachers when I was going through medical school. They actually taught me neurology, and now to be able to collaborate with them is great. So we have major collaboration where we actually got a grant through the Motor Neuron Disease Association for checking 100 what we call whole exomes, which are the entire genetic material for all the genes that code proteins within the body.

Barbara Sofer:

You can do that here at Hadassah, is that right?

Marc Gotkine:

We can do it in Hadassah, and this is done very frequently in Hadassah, and we send a lot of tests to be done in Hadassah. That specific grant meant that we were getting them done in London, but through that collaboration we've discovered some new genes, new mutations and some potentially new genes that could be responsible for ALS. The reason why it's especially important to focus on the patients in Israel rather than anywhere else in the country is that we actually have a few features of our patients somewhat different to patients around the world, in that there is a tendency, at least in some populations, some more than others, for the parents to be related in some ways. So there are some communities where it's ...

Benjamin Cohen:

Like first cousins or something?

Marc Gotkine:

Exactly, like first cousins, even second cousins. And even without that you will have ...

Benjamin Cohen:

My grandparents were first cousins. It wasn't always a strange ...

Marc Gotkine:

Exactly. We have some Ashkenazi patients who, their parents were first cousins. I think that it's slightly less common now in the Ashkenazi community, but certainly within the Arab community and certain Sephardi communities or North African communities, that the previous generation were still marrying within their family, first or second cousins. So that actually was the impetus to do the initial collaboration, to focus as much as possible on patients who, their parents were related in some way. And actually, through that approach we found quite a few potentially new mutations that could be only causing ALS when you get a double copy. Because the problem with people who, when they're related getting married and having kids, is that if there's a disease that requires two copies of the gene, one which you get from your father, one from the mother, then there's a much higher chance of the person getting two problematic or "bad" copies of the genes, and that can cause a disease.

Marc Gotkine:

So this is very well established in other diseases like Riley-Day or Tay-Sachs, but ALS is obviously a disease where there are lots of different factors and lots of potentially different genes. But the hypothesis that drove this research that we had many years ago was that even within people with ALS we're going to find that if their parents are related, it could very well be that their disease is being caused by a double dose of a problematic gene.

Benyamin Cohen:

It's interesting, we've spoken to several doctors on this show that have talked about doing research based on the fact that the ... It's aided their research, the fact that the husband and wife have some kind of relation.

Marc Gotkine:

Right. So that's actually one factor that that very much helps genetic research in general in Israel, and specifically within the field of ALS. The other thing that we all know very well – from whoever's visited Israel knows, whether it be within the Arab population or the Jewish population – we have a lot of families who have a lot of kids. And if you're doing genetic research and you have a single child it's difficult. If there's two or three in the family it's often not too easy, but if you have families where people are having nine, 10, 11 kids, and that's really not that uncommon here, then this can actually really, really help you pin down the genetic cause of a disease. And we've very much benefited from that feature of the Israeli patient population.

Benyamin Cohen:

And Hadassah is a multicultural hotbed.

Marc Gotkine:

Exactly. It might not be clear for people outside of Israel, but we in Hadassah see many, many Arab patients. I see many patients from East Jerusalem, even from the north of the country. And I have patients from Saudi Arabia who end up coming here, many patients as well from the Palestinian Authority come to see me. And in fact, the paper that we're just about to submit with the team from London about a new mutation is about a family within the Palestinian Authority that we were seeing. And actually there were a few members of the family who unfortunately were affected and have passed away from ALS, but they were very forthcoming in helping us with our research.

Barbara Sofer:

I once took someone around from a very big center in the United States, and he said that you can do genetic research here so much faster and so much better and so much cheaper, even, than they can do it in the United States. So that he really gave me an incentive to tell people that they should concentrate a lot of their research here because we have that capacity and we have an advantage because of this treasure.

Marc Gotkine:

Exactly.

Barbara Sofer:

Is that correct? Would you agree with that?

Marc Gotkine:

I think that's absolutely true, and I would say even more than that that I think that in general people are becoming better educated as to the problems with what we call consanguinity, or marrying someone within the family. And that's a good thing, because we want to try and decrease the amount of diseases that could come about. But on the other hand, it means that now is the time when the next generation isn't going to have the same situation because this consanguinity, this marrying within your family, is going to be much less. So it's not something that we can defer and say, "Well, in 50 years, in 100 years we'll do the research." It has to be done now because now is probably the last generation where we're going to see a significant amount of this consanguinity.

Marc Gotkine:

And especially even if we take the Jewish population, that made aliyah, so where they were coming from areas where they might have been in villages in Iran or Iraq, or may have come from communities in North Africa where they weren't necessarily marrying people that they knew were their first cousins, but they were staying within their own small Jewish population within those other countries. And even in that case we're seeing some of these double doses of genes appear in patients with ALS. But nowadays it's like everyone knows, and it's a great thing, there's Ashkenazim marrying Iraqis and there's the whole melting pot, which is a great thing that happens in Israel.

Marc Gotkine:

But on the other hand, and it's good for preventing these genetic conditions in the next generation. But it's going to mean that the next generation won't have this research ...

Barbara Sofer:

Advantage.

Marc Gotkine:

... Advantage or this research resource that we have now. So now is the time that it has to be done.

Barbara Sofer:

And stem cells?

Marc Gotkine:

So stem cells are another very promising area within ALS. Hadassah was involved with the first phase of the BrainStorm trial that was led by Professor Karoussis. And now I'm the principal investigator of Kadimastem trial, which is ALS trial on human embryonic stem cells. And that's very exciting. So that's the first in human trials actually going on right now.

Benyamin Cohen:

When we return Dr. Gotkine talks about what it's like to break life-changing news to a patient. Plus, he explains the strange story of why so many people with ALS are former triathletes.

Marc Gotkine:

The message definitely isn't, stop exercising or stop doing triathlons, or even to be concerned if you do, but it's interesting and I think that it's just a tool by which we can try and understand the mechanisms of the disease.

Benyamin Cohen:

All that and much more after the break. It seems that news headlines about the coronavirus are changing by the hour. Keep up to date with everything that Hadassah Hospital is doing to help combat this deadly disease. To find out how we're dealing with the crisis visit our website at hadassah.org/CovidUpdates. We're posting frequently about how our doctors, nurses, and researchers are working to fight the further spread of COVID-19. You can also follow Hadassah on our social media accounts on Facebook, Instagram and Twitter. Also, we're looking to you, our listeners, for which medical experts you'd like to hear from in the weeks ahead on this podcast. Please let us know by sending an email to us at marketing@hadassah.org. That's marketing@hadassah.org. And now, back to our conversation with Dr. Marc Gotkine.

Benyamin Cohen:

About 10 years ago you helped establish the Hadassah ALS Multidisciplinary Clinic.

Marc Gotkine:

Yeah, that's right.

Benyamin Cohen:

Can you tell us what happens at that clinic?

Marc Gotkine:

So the clinic is one which is specifically for people with ALS, people who've already received the diagnosis. And the idea is that people who have ALS shouldn't have to wait a long time and that they should get to see people who are experts in the field. And where possible, if they need multiple medical professionals to be involved ...

Benyamin Cohen:

From different fields.

Marc Gotkine:

They should be able to do it as a one-stop shop. So when we established it, the idea was that people would come and they would see a physician, that was just me at the time. Thankfully we've grown since then. Then there's a nurse who's involved, they would do respiratory function tests. As I mentioned, the respiratory muscles are affected, so they would do some tests to see what the situation was with their respiration, see a pulmonologist who would give them advice about respiratory treatments that they might need, a social worker. So they would be able to come and receive advice in various fields. In addition, it's the center for a lot of different research projects like the genetic project that I mentioned. Of course, the project that we perform with the Weitzman Institute on the bacteria within our gut that might be having a role in ALS in humans.

Marc Gotkine:

These types of research are only possible by having a dedicated ALS center. And actually, all the patients who come, they're very, very helpful and they want to be involved in research, even if they know that it's not going to help them themselves. They're almost always agreeing to participate in genetic research. They're giving blood samples, other research on what we call biomarkers, which can maybe plot the ... Which can maybe help us predict which patients are going to progress faster, which slower. And also, one of the key elements is that we actually built a dedicated database of our ALS patients, which actually, every single piece of information about the clinical progression and possible risk factors were entered into this database. And through this we've actually managed to complete studies, for example, we looked through the database and saw that we had a lot of triathletes.

Benyamin Cohen:

Yeah, I was going to ask you, I saw that. So we talked about how genes are one predictor, but if you're a triathlete, that may be another predictor?

Marc Gotkine:

So we definitely found that if you look at the general population and then you look at the population of people with ALS who came to the clinic, we had a vastly overrepresented number of triathletes in the ALS population compared to what you'd expect. Now, that doesn't mean that doing triathlons will cause ALS. It doesn't mean that at all. But I think that it's definitely possible that whatever genetic factors mean that someone is going to be very successful in endurance sports such as triathlons, perhaps those genes themselves are actually related to ALS in some way. So the message definitely isn't stop exercising or stop doing triathlons, or even to be concerned if you do, but it's interesting. And I think that it's just a tool by which we can try and understand the mechanisms of the disease.

Benyamin Cohen:

Are there other subpopulations besides triathletes that you've noticed?

Marc Gotkine:

So actually there have been numerous publications around the world about soccer, what we call football, but soccer professionals being affected more.

Barbara Sofer:

I've heard that American football, where you have so many blows to the head ...

Marc Gotkine:

Sure, right.

Barbara Sofer:

Is that true?

Marc Gotkine:

So I think that there's definitely been some research that suggested that as well. I think in those also Parkinson's was perhaps somewhat overrepresented. But yeah, so I think that this isn't something that's specific to any kind of sport. It might be just to do with endurance sports of any kind.

Barbara Sofer:

If you had a family member who wanted to play professional football in the United States, would you be against that? Do you think that's dangerous for the brain?

Marc Gotkine:

I'd probably be against it, but not because of the risk of getting any of the diseases. But no, look, I think that sport, the health benefits of sport, they vastly outweigh any of the possible and definitely not proven detrimental effects in terms of neurological disease. I think that people should continue doing sport and definitely shouldn't misapply this research in order to make a case against doing sport.

Barbara Sofer:

Even the sports that have trauma to the head?

Marc Gotkine:

Well, I would generally avoid that for sure. I would personally avoid sports which involve head trauma, but I'm talking about the other endurance sports like triathlon and tennis or ...

Benyamin Cohen:

Right, ping pong is probably safe, I'm guessing.

Marc Gotkine:

I would assume.

Barbara Sofer:

I don't know if the ophthalmologists would agree, because you get a ping pong ball in the eye, it could be very painful and dangerous, right?

Benyamin Cohen:

Right. obviously we're making some jokes now, but ALS, as we all know, is a very serious subject. And I can only imagine how hard it is for a doctor to walk into a room and break the news to the patient, to the family, about a diagnosis of ALS. How do you go about doing that?

Marc Gotkine:

So it's definitely challenging, but I do see it as a very important challenge. I think that the way that it's brought over initially is actually going to very much dictate the state of mind of the patient and their family throughout the entire course of the disease and how well they'll be able to cope with it. We actually published some research to show that having an optimistic outlook and that being hopeful is very, very much important to maintaining quality of life in ALS.

Benyamin Cohen:

More so than other diseases?

Marc Gotkine:

I think that definitely it has a big effect in ALS. I think that in certain other diseases it could be, but we obviously just checked within ALS. So I think that for that reason it's very important to do it in the right way. And I see it really as a process. I think that it can't really be done as a one-time thing, that someone comes in, you meet them for the first time and drop a load of bricks on them. It really mustn't be like that. I think that it's important that you start the diagnostic process, that you explain that there's certain options, and that they have time to digest the information over time. And it varies, I don't have a set way of doing that. It's about gauging who the person is in front of you, what's important to them.

Benyamin Cohen:

So if you and I were to have this conversation again in five or 10 years, where do you hope to be as far as your research with ALS? And not having a cure for it, but ...

Marc Gotkine:

I think that for sure I would expect that there'll be one or two stem cell therapies that hopefully will be approved for regular use by then. And I wouldn't be surprised if one of the therapies was from Hadassah, one of the ones that went through trials in Hadassah. As I said, now we're doing the Kadimastem trial. And we're hopeful, it's very early days so we don't have any concrete results, but we're very hopeful that we'll be able to move forward with that. There are the non-stem cell therapies that we're checking that hopefully will be found to be helpful. And I think the approach will be a cocktail approach. So similar to HIV and AIDS or in oncology, where you find one drug, then you find another drug, and it's going to be, every time we find something that can slow down the disease we'll add it to the cocktail. And by that means we'll be able to extend the survival and people will be living a lot longer with the disease, and their disability will be progressing slower.

Marc Gotkine:

But I think that one of the most exciting areas for us is the genetic research that will have discovered many, many more new genes. And we'll have treatments which are gene specific that will be able to slow down the disease dramatically, depending on what genes are affected in any specific person. So it will be very much personalized medicine in terms of the genetics. And we'll also have the very exciting recent research that we did about the microbiome, about the gut bacteria that have been shown to be important in many different conditions in obesity, diabetes, and now, for the first time, there's some strong evidence that in, at least in the mouse model of ALS and perhaps also in human ALS, where we found some similar differences and changes in the gut bacteria, that actually we may be in the future able to manipulate the bacteria within our gastrointestinal system in order to help people with ALS and slow down progression.

Barbara Sofer:

Obviously you could have stayed in London, everybody would be lucky to have you, and we're very happy that you made aliyah and that you're here at Hadassah Medical Organization. When you look back at that decision to leave England and to come to Israel, was it a good decision for you?

Marc Gotkine:

It was a great decision. I have no regrets. So we're very happy here. When I came, my parents were, "Well, you could have such an easy career." Everything was sort of laid out for me in London, I had job offers, and isn't it a shame to go to Israel where you could just be so successful in London? And obviously I was a Zionist and loved being in Israel, even also just from my personal enjoyment. And so I would say that in no way has my career been adversely affected. The opposite, I think that the opportunities that I've had in Hadassah have been incredible and I'm very happy to be here. And I'm collaborating with my teachers from London and collaborating with teams, excellent teams within Israel and outside of Israel. So I think that really there are definitely, as I mentioned, there are opportunities here that I wouldn't have had in the UK. So yeah, in summary, I'm very happy to be here.

Benyamin Cohen:

Dr. Gotkine, thank you so much for taking the time to chat with us today. We really, really appreciate it.

Marc Gotkine:

Thank you for having me.

Benyamin Cohen:

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