Dr. Michael Levy’s Research at The NMO Clinic and Research Laboratory at Mass General

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GG deFiebre: [00:00:00] Hello everyone and welcome to the SRNA Ask the Expert Podcast Series: Research Edition. Today's podcast is entitled "Dr. Michael Levy's Research at the NMO Clinic and Research Laboratory at Mass General." My name is GG deFiebre, and I moderated this podcast with Dr. Levy.

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[00:01:34] For today's podcast I was joined by Dr. Michael Levy. Dr. Levy specializes in taking care of patients with neuro-immunologic diseases, including multiple sclerosis, transverse myelitis, optic neuritis, and neuromyelitis optica. In 2009, Dr. Levy was appointed to the faculty as Assistant Professor at Johns Hopkins, where he started the neuromyelitis optica clinic and research laboratory. And in 2019, he moved to the Massachusetts General Hospital and Harvard Medical School to develop the research program in neuroimmunology.

[00:02:03] Thank you for joining us today to talk about your research and what you're working on currently. I'm here with Dr. Michael Levy. To start, can you just talk a bit about what you're doing right now in terms of tracking COVID-19 vaccines?

Dr. Michael Levy: [00:02:16] Yeah. This study came out of a bunch of questions from patients who are understandably concerned about getting a vaccine and specifically about whether the vaccine would be effective, but more importantly, is it safe for them? On the efficacy side, I think a lot of people have been sheltering in place, avoiding contact, doing all the social distancing that they need to do. And so I don't think that efficacy is number one on their consent. It's not like, you know, everyone has been trying to get back to normal life ahead of anyone else. But there is a valid question about whether medications like rituximab, CellCept or, or any other immune suppressants would interfere with the vaccine. And for both of the Moderna and Pfizer vaccine trials, they excluded people who were on these drugs because they didn't want it to affect their efficacy.

[00:03:15] So we just don't have the data. Now, what I've been recommending to people is that based on other vaccines where we have data, we know that there is some decreased efficacy, at least in terms of antibody production, but that's not the only form of protection that you get from a vaccine, especially from these new RNA vaccines, where we think T-cells might be important and we don't really suppress T-cells in these diseases.

[00:03:41] I think on the efficacy side altogether, I would still recommend patients go get the vaccine. I think it's likely to be effective. And on the plus side, each of these two vaccines requires a booster. Three weeks for Pfizer, four weeks for Moderna so that if the first one was not sufficient, hopefully the second one will be.

[00:04:02] Now they're even talking about a third one with Moderna depending on the strain of coronavirus that you're exposed to. So I think there'll be opportunities for more improvement on the efficacy side. On the safety side in the Pfizer trial, there were three immunological events. They're all Bell's palsy, which is an inflammation of the facial nerve. It causes weakness on one side of the face. And that, it wasn't clear. It was a little more than it should be in the general population, there were not in the placebo arm. But three out of I think it was 15,000 in the, in the vaccinated arm is not that unusual. So we were watching it. We wanted to see what would happen with that in the, in the real world.

[00:04:44] And now after millions of doses administered, we haven't seen any immunological signal. In fact, I just had a meeting with our leadership at the hospital and I asked our lead COVID person there if there were any immunological signals at all that we need to be concerned with, not just Bell's palsy, but anything else? And she said, no, she hasn't seen anything either. Now, if you, if you're familiar with the AstraZeneca vaccine, the one that was being developed at Oxford, there was a case of transverse myelitis in a previously healthy person. And then there was one case of transverse myelitis that turned out to be MS that was newly diagnosed. So both of those events happened with the, with a strain of adenovirus. In the case of AstraZeneca, they're using a chimpanzee adenovirus, that's re-engineered to express the coronavirus spike protein. The virus itself, it cannot replicate, it cannot infect, but it's used to stimulate an immune response, and the spike protein for coronavirus is included among those.

[00:05:49] But live viruses are generally more stimulating than this RNA vaccine. And so, if you want to play it super safe and you have the opportunity to pick your vaccine, which many patients don't, but if you did, I would pick the RNA vaccine because we don't seem to see any immunological events. If you only have access to AstraZeneca, I think the risks are still very, very low for triggering a relapse or for triggering a, an attack. So I would still, probably on the balance of risk, especially if you're older, you have other comorbidities, it's still probably in your best interest to take the vaccine.

[00:06:28] And I should mention one more thing that we are tracking side effects. All these recommendations are great for patients, but we don't have data to support them yet. And so what we are doing is we're collecting survey data from patients. There's a link through SRNA. There's a link through my Facebook page. There's, I think the Sumaira Foundation may have posted a link. And it takes you to a page where you get to put in

your information and whether you've had the vaccine and whether you've had any side effects. And so far we've had about a hundred or so who have been vaccinated once at least and some twice. And we've only, we haven't had any immunological events so far out of a small number of patients, but one person had a worsening of her neurological symptoms, an NMO patient. And it felt worse afterwards. And that's not unusual that after an intervention, like a vaccine, that you might feel a little bit of your old symptoms come back, but it wasn't a relapse.

GG deFiebre: [00:07:26] Right. And even though those numbers are small, I mean, with a rare disease, you know, a hundred is still better than none. So it's, it's great that you're collecting that information and hopefully more people will fill it out as, as we go forward.

Dr. Michael Levy: [00:07:38] That would be great.

GG deFiebre: [00:07:39] So, in addition to that, I know you're also working on some transverse myelitis research. Do you mind talking a bit about that as well?

Dr. Michael Levy: [00:07:47] Our transverse myelitis research came from two sisters who both had transverse myelitis, and we were interested in finding a gene that could be responsible.

[00:07:57] And we worked with the Johns Hopkins and Baylor College of Medicine genetics team, and they narrow it down to one gene that was different between these two sisters from their healthy siblings. And the gene is called VPS37A. We weren't sure exactly what to make of it at the time, because we weren't really sure what this gene even did, it was really just a broad screen to look for genes that could be involved. And the first thing we did was we screened more patients, and we happened to find the exact same mutation in another woman with transverse myelitis. And so then we got interested in it because that would be kind of unusual. As it turns out a, in all of the genetic databases all over the world - and there are millions of people who've been sequenced through ancestry and national geographic and, and all of these data are compiled together - we couldn't find a single other person in the world who had the same genetic mutation. So we thought, well, that's interesting. Three people all had transverse myelitis with a mutation never seen before. So we started looking for other mutations, and while we couldn't find any other patients with that specific mutation, we found a total now of at least eight people who have mutations in other part of that gene. Now, that gene is interesting, it's involved in what's called vesicle recycling. So when you have a cell and it has something on its membrane, when it takes that thing in to interrogate it, it has to transport it to some intracellular machinery and then it transports it back out to the membrane

[00:09:37] VPS37A is involved in that transport. So we're not exactly sure how transportation of this vesicle is involved, but when the, when the body is exposed to viruses and two of the things that always takes it up brings it inside for interrogation. And if there's some sort of disruption in that, then perhaps the immune system sees that disruption as, as an infection or perhaps it creates some sort of new protein complex that's not seen before, and then the immune system reacts to it.

[00:10:09] Now, what's interesting about it is that this mutation seems to only be associated with the monophasic transverse myelitis. Even though the, these people have the mutation their whole lives, they only have one attack. So even with that mutation, it seems to be a pretty rare event.

[00:10:27] Now, one of those women with the transverse myelitis genetic lesion, she happened to pass away. She died from a gastrointestinal infection. And the family was gracious enough to send us her tissue so that we could study it further to really understand how this gene is involved. We have her spinal cord, we have the lesion itself. So we're going to take a really deep look at this lesion to understand how this gene is

involved. Because if we can understand how monophasic transverse myelitis happens, we might be able to prevent it or treat it better.

GG deFiebre: [00:11:02] Well, thank you for that summary. It's really interesting and, of course, very gracious of that family to do that as well. So, looking forward to learning more as you, as you work on that. So, I know you're also working on NMO research as well. So if you could talk about that, too.

[00:11:18] **Dr. Michael Levy:** [00:11:18] Yeah, our NMO research and our transverse myelitis research uses animal models to try to understand these diseases. For transverse myelitis, we've knocked out the gene - that VPS37A gene that we found in people - we've knocked it out in mice as well. It turns out it's lethal. If you don't have that gene at birth, those mice do not survive. So we created what's called an inducible knockout. So these mice are born with the gene so they can express it normally and develop up to a certain age. And then we give them a medication that knocks the gene out. So then they become essentially mutants for that same mutation. And so now what we're doing is we're confirming that this model works. That's the first thing we're doing. And then we want to see how susceptible these mice are to transverse myelitis.

[00:12:06] With neuromyelitis optica, we use a different genetic approach, in which the aquaporin-4 gene, which is the target of NMO, that gene is knocked out. And in those mice, then they think aquaporin-4 is a foreign protein. And so it's easy to create an immune response to it that mimics what happens in humans.

[00:12:27] Now, of course, people who have NMO, they still have their aquaporin-4 gene, but for whatever reason, the immune system does not recognize it as self. And so what we're doing in these mice that don't have aquaporin-4, we're trying to teach them, to teach their immune systems, that aquaporin-4, in fact, is self. It is a protein that they should consider harmless, not harmful, and they should not attack it. And this process is called tolerization. And we're hoping to apply it to people who have NMO, whose immune systems think that aquaporin-4 is foreign.

[00:13:01] And the goal is to reteach, reeducate the immune system about just this one problem. Because people with NMO, well some of them, have overlapping autoimmune diseases, but many of them don't. And the only problem is that their immune systems are dysfunctional only towards aquaporin-4. So if we could really focus in and re-educate towards that one outcome, then we don't have to suppress their immune systems globally or with medications on a regular basis. So that's the goal of tolerization therapy.

GG deFiebre: [00:13:34] Great. And then for people who may have been diagnosed with MOG antibody disease, do have research on that as well?

Dr. Michael Levy: [00:13:40] Yeah. The interesting thing with MOG antibody disease research is that the MOG mouse model has been around for decades. And people used to - as they did for many, many years - confuse MOG and MS. So MOG antibody disease patients have optic neuritis, they can have brain lesions, transverse myelitis... It's very, very similar clinically to multiple sclerosis. And so, only in the past few years have we been able to distinguish these patients with the MOG antibody test that's been available in the US since 2017 and in the UK since 2015. And turns out the mouse model for MOG is a much better model for MOG than it is for MS, as we figured.

[00:14:23] So we're using this MOG mouse model. There's already been a ton of research on it, as people have been doing studies in MS, but what they were really investigating is MOG antibody disease. So we have the benefit of all that previous research. And so now we're going back and we're saying, okay, now through the lens of MOG, how do these MOG animal models make sense now?

[00:14:44] And one of the things we've been narrowing in on is this one cell type called a Gamma delta T cell. It's a type of T-cell that is not the prototypic type of T-cell that you may hear about that's involved in coronavirus vaccine reactions, and so on. It's really a unique type of T-cell. It's only involved in a few immunological processes. And we think these Gamma delta T-cells may be involved in MOG.

[00:15:09] They live in the meninges around the brain, where we see a lot of enhancement in MOG antibody disease. Even though there's no MOG there, there's still an immune reaction there. And people have asked: well, why? And maybe the reason is that these Gamma delta T-cells, that's where they live. And then when they invade, they cause optic neuritis and transverse myelitis just as they do in the mouse model. And these Gamma delta T cells are critical in the mouse model. So what we're trying to do is figure out how these cells are activated? How they decide to attack? Why do they go to the optic nerve? Why do they go to the spinal cord? And how can we prevent that from happening?

[00:15:45] One of the interesting things about MOG antibody disease is some people just have a monophasic condition. One time attack, maybe optic neuritis, maybe ADEM, and then it never comes back, and the antibody goes away. And why is that? Why doesn't it establish a more long-lasting immune response just like aquaporin-4? We've never seen a case of aquaporin-4 spontaneously resolve. So, understanding the differences between these two diseases using the mouse models, it's really helping us understand human disease.

GG deFiebre: [00:16:16] Great. Thank you for that overview. It all sounds very interesting and so we look forward to, as you learn more, learning more as well. Is there anything else you wanted to talk about or mention in terms of the research you're doing or?

Dr. Michael Levy: [00:16:29] Well, we are, we are doing more research in MOG on the clinical side. So everything that I've told you we're doing in the lab. But we also have some clinical trials launching, specifically for MOG. We're hoping to do two trials coming up this year in partnership with companies that own the drugs, and we're helping them develop it towards MOG antibody disease. Because right now there's no FDA-approved drug for MOG antibody disease. So it would be nice if we could, if we could create a drug. All while we're trying to understand it and apply tolerization therapy, at the same time, we're working on drugs to help minimize the damage from these attacks.

[00:17:08] The other things we're doing: we have a diet study that's going to launch soon. I think most people feel like there's a link between their diet and disease. And I feel it too. I mean, I don't have an autoimmune disease, but from all the times patients have told me about how diet affects their daily lives and how it affects their immune system. This is something that needs to be looked at. So, we've partnered with a dietician nutritionist and we're putting together a survey to just begin to scratch the surface. And we're going to use it for, for all of our patients: NMO, TM, and MOG. And then we'll go from there. And I think that there's just a lot of different ways to look at this from a diet perspective, and this is just really the beginning of it. So, if we find certain things that seem to correlate well, then maybe we'll pursue that. And if other things come up, then, you know, we may take a different turn. But those studies are coming very soon.

GG deFiebre: [00:18:07] Great. Yep. And we will certainly share information about it once, once it's ready to launch and everything. So, yeah. Well, thank you so much for joining me today. I think this was a really good overview and it's great for people to hear what's, what's going on in the research world. So thank you.

Dr. Michael Levy: [00:18:21] Thanks for having me.