

# Unlocking controversies around causation

The role vaccinations, infections, environmental triggers, and genetics play in ADEM, AFM, MOGAD, NMOSD, and TM

You can view this presentation at: [youtu.be/QY0qETUNmEY](https://youtu.be/QY0qETUNmEY)

[00:00:05] **Dr. Benjamin Greenberg:** So, while in the world of politics, in the Supreme Court, things like affirmative action, diversity are controversial, here at UT we believe in it. So, we invited somebody from a smaller, lesser-known institution to join us in Dallas. Michael Levy from a small school called Harvard, the UT of the North, Mass General and Harvard. Mike Levy to join myself. We're going to have a conversation. We're going to take a seat at the table. Some of you may know this, Michael and I went actually to medical school together and even then, I knew he was the smartest one in the room.

[00:00:49] So, the rule for this session is I get to ask all the questions and he has to give all the answers. So, Mike, come on up. So, I like the title for our session. Can you guys hear coming through? Okay. Unlocking controversies around causation, the role of vaccinations, infections, environmental triggers and genetics. The role they play in ADEM, AFM, MOGAD, NMOSD and idiopathic transverse myelitis. This is clearly not a controversial topic at all. There has never been a Facebook post around causation around any of these things.

[00:01:46] But in every symposium I've ever taken part in at some point this question comes up. What caused and then fill in the blank whatever the diagnosis is. So, I'd like to start, as I said, I'm asking the questions with the notion of autoimmune diseases in general and not pick any of the specifics and just get your thoughts, Michael. If you had to give people a construct of how we think about why some people's immune system, not only gets confused which is pretty common in humanity, most of us have evidence of autoimmunity in us. But why do some people's confused immune system go on to actually have an attack? What's your conceptualization just in general of the arithmetic? What are the variables that go into it?

[00:02:33] **Dr. Michael Levy:** Well, if you look back historically, the idea that the body could attack itself was not widely accepted at all. In Greek times, it was considered heresy to even consider that. And it wasn't until the mid-1900s and thyroid disease that people started suspecting it and proposing it. And even then, the

doctors were considered crazy for thinking about the idea that the body could be attacking the thyroid gland. But we've come a long way since we know that the immune system has a really difficult task. It has to rid the body of infections that are foreign, has to recognize when cancer which is coming from your own body also needs to be destroyed and it has to preserve all the normal tissues.

[00:03:21] This is a really hard thing to do and the immune system is well trained, but it does make mistakes. And there are known examples where you could fool the immune system into attacking itself by you can either do this, you could manipulate mice to do this. We have human examples of this. So, the idea that the immune system makes mistakes is not crazy anymore. We accept it now, but the question is why does it happen? And why does it happen in such stereotypical ways?

[00:03:47] So, if there are two people here who have MOG antibody disease, you both now have immunity against this MOG protein. Well, what triggered it? What do you two have in common that created your immune response to MOG? Because that's really what we want to try to understand and the more we understand about these diseases and what their target is, the more we can then work backwards from that. Well, what kind of proteins look like MOG? We have lots of proteins in your body that look like MOG, but the immune system doesn't attack those.

[00:04:17] Why not? And where else could MOG have come from something that looks like MOG that fooled your immune system. We don't know. And then NMO we have the Aquaporin-4 target. We know that the immune system attacks Aquaporin-4 but there's Aquaporin-4 throughout your whole body, in your lung, in your stomach and the immune system leaves it alone there. But Aquaporin-4 in the spinal cord there it attacks. So, why does that even happen? We don't know. These are very complicated questions.

[00:04:46] **Dr. Benjamin Greenberg:** So, I'd like to set the stage with some thoughts and language around this. So, that as we formulate our ideas around causation, we're all speaking the same language because this is a complicated topic. So, first, I think it's important to understand that in the immune system which as Michael said is on the attack, fighting not just infections but fighting cancer cells, the immune cells go in and out of all tissues in your body all the time looking for problems, looking for things to solve. And inflammation over the years has gotten a bad rap.

[00:05:22] Inflammation is lifesaving. So, if you've ever cut your hand and the next day it's swollen, that's inflammation, those are immune cells leaving the bloodstream, entering the tissue and fighting off the bacteria that are trying to invade through that skin. So, inflammation is a wonderful thing when it's there to fight an infection or fight a cancer. If the inflammation occurs for the wrong reason or the wrong target, that's when it's a problem.

[00:05:47] And in our world, particularly when we're talking about certain diagnoses, there's some confusion around what I refer to as specific or non-specific inflammation. So, in an autoimmune disease and in our world, anti-MOG associated disorder, neuromyelitis optica are the kind of foundational examples of autoimmune disease because we know the target, we know what the immune system got confused about. The immune system goes in and causes damage.

[00:06:14] There is also what's called a para-infectious inflammation which can cause damage. So, how many people here have cut themselves or skinned their knee and has a scar left behind. So, I tried to chop off my finger it didn't work, but I'm left with a scar. I will not use a mandolin to this day in the kitchen. But that is evidence so that inflammation that occurred after my injury was there for a good reason to fight bacteria, but it altered the skin forever.

[00:06:46] So, sometimes if you get an infection within the spinal cord, our classic example is AFM where a virus enters the spinal cord, the immune system going there is not an autoimmune disease, it's there to actually fight an infection, but in the process causes damage to the tissue around it. So, in some of the conditions we work with, there's true autoimmunity and sometimes it's just friendly fire in the course of fighting an infection.

[00:07:12] So, when we're talking about autoimmune conditions and the triggers for confusion, we have to go one by one through each condition to try and figure out why did that immune system get confused? And in my conceptualization, it's the stars aligning in the wrong way. You need the right person or the wrong person whose immune system is prone to confusion, is easy to confuse and the right trigger at the right time. So, I can take people who are genetically identical, give them the same exposure on two different days and they'll have two different outcomes.

[00:07:51] It's not just what we get exposed to, it's in what context and what time and what was happening in our life. And I think most of the evidence we have for this comes from the literature on multiple sclerosis which shows there are certain risk factors. One infection that gets a lot of attention is Epstein-Barr virus that everybody gets exposed to. We've all been exposed to Epstein-Barr virus, but it's how old you are when you get exposed that dictates your risk of multiple sclerosis.

[00:08:17] So, the reason it's hard to do these studies in rare disorders is if there is a common exposure, it may have one impact on one person and a different impact on another person. And so, these studies are very difficult to do, but I'd like to walk us through the evidence we have around specific ones and I'm going to start with something that's near and dear to your heart. Let's talk about the genetics of things and I want to break it into two parts. One is genetic causes of these disorders versus genetic risk factors. And can you walk us through what the difference is between those two and what we know?

[00:08:53] **Dr. Michael Levy:** Genetic causes would be a genetic mutation that leads to problems in your spinal cord that should happen no matter what the environmental triggers are. So, these would be passed down from generation to generation or there may be some difference in penetrance and how likely you are to express those genes. But in general, these are things that run in families. So, often you'll hear of family history and then you can run a genetic testing and find the mutations. So, that's really the causative factor in leukodystrophies and other genetic illnesses.

[00:09:34] The other category of genetic involvement in these conditions is a predisposition. This is just how your immune system is prepared and set up to fight infections and what that means in the context of immunity. So, for example, if you consider there's a part of Africa called the meningitis belt, where meningitis runs rampant and people who live there, who have a certain mutation in their complement gene are protected against meningitis. But when they leave Africa and come to the United States, that gene may predispose them to NMO. And so, it's protective in one context, but it could be harmful in another context. And that's the genetic predisposition that we're talking about in terms of autoimmunity.

[00:10:21] **Dr. Benjamin Greenberg:** And so, it's that notion of the right host and the right exposure leading to [that]. So, let's talk about the environmental trigger side of things. Now, when I say just out of curiosity, when I say environmental triggers, what comes to mind for you in the audience? So, an environmental trigger of an autoimmune disease.

[00:10:39] **Audience Member 1:** Pollution.

[00:10:40] **Dr. Benjamin Greenberg:** So, pollution, something in the air.

[00:10:44] **Audience Member 2:** Infections.

[00:10:46] **Dr. Benjamin Greenberg:** So, infections and we'll carve that one out. What is it?

[00:10:50] **Audience Member 3:** Food.

[00:10:50] **Dr. Benjamin Greenberg:** Food. I like food.

[00:10:53] **Audience Member 4:** Chemicals.

[00:10:53] **Dr. Benjamin Greenberg:** Chemicals. I'm waiting for my favourite.

[00:10:56] **Audience Member 5:** Vaccines.

[00:10:58] **Dr. Benjamin Greenberg:** Vaccines, we will get to although those aren't floating in the environment. Someday, maybe they will. Any others?

[00:11:07] **Audience Member 6:** Water.

[00:11:09] **Dr. Benjamin Greenberg:** Water, one that I get asked a lot, but it's usually third visit or later. So, it's interesting we've talked about this a little bit. There are understandably certain questions that come to mind the first time you meet with a neurologist around one of these conditions. And then the questions evolve and third visit and later, I get asked, especially in our children's clinic a lot about mold exposures in the environment and whether or not there's black mold, maybe that's just a Texas thing or Louisiana, Mississippi thing, I don't know. You don't have mold in Boston, do you? So, when you think about environmental, food, and diet. Are there things that are on your list in terms of risk factors that we think about for autoimmune diseases?

[00:11:58] **Dr. Michael Levy:** Well, you mentioned Epstein-Barr virus and multiple sclerosis. You have to have an Epstein-Barr virus infection to get multiple sclerosis. It's absolutely required. So, one of the things that we were looking at is in MOG disease where a lot of kids have it. We started looking at those patients and we don't see that everybody has Epstein-Barr virus infection. So, we think that those are really distinct. One condition really depends on it. One does not at all. So what do these kids have?

[00:12:26] They have all kinds of different infections as you'd expect. I have three kids, they're chronically infected and, but we don't know which one is triggering MOG if any. It might be one of those things where if you get that cut on your finger in the kitchen and then you rub jalapeno peppers on it. It's not that the jalapeno is making the inflammation happen, it's just making it worse. So, maybe in the context of infection, the MOG gets worse, but maybe the infection is really not the trigger. These are things that are really hard to sort out.

[00:12:59] **Dr. Benjamin Greenberg:** So, and let me just expand on that in terms of this notion of an infectious slang. I'll give you two examples to think about as you're contemplating risk factors. So, one model is your body gets an infection, the immune system fights it off and then in the aftermath goes hunting just to make sure it got rid of it. And when it peaks into the spinal cord, there's something there that is reminiscent of that infection. It's like the worst eyewitness in FBI history, you know, it goes and like that's the guy.

[00:13:32] That's absolutely top down and it goes on the attack, but it wasn't the actual villain in the story. And so, that's a post-infectious autoimmune disorder. And it's just because there was something similar. There's another version of this story that we've now parsed out in an autoimmune disease of the brain called NMDA

receptor encephalitis. Did anyone read the book or see the movie Brain on Fire? So, that's what this is about. Brain on Fire is about a young woman who developed encephalitis because of an autoimmune disease. And what we found in a large number of people with NMDA encephalitis is they're perfectly fine, perfectly fine.

[00:14:14] And then they have a member of the herpes family of viruses go into the brain and cause encephalitis. The immune system goes to fight it. And while there gets sensitized to a brain protein and then comes back later as NMDA encephalitis. So, it's not that the herpetic virus looked like the NMDA receptor, it's while those forces were in the brain, they got confused about a totally separate crime going on a totally separate protein. And so, in one scenario, it's a systemic infection that then confuses the immune system and the other, it's a local infection that attracts the immune system and in the course of that event gets confused.

[00:14:57] And so, when we're doing these studies, it makes it really difficult again with rare disorders to try and figure out what happened in each person that could lead to the confusion of the immune system. And we get asked the question a lot. Can we go back and never figure out what the trigger was? My unfortunate answer is for an individual sitting in front of me today, the likelihood is no, but we're hoping to do studies to fill in gaps for some folks in the future. And it wouldn't be a talk about controversies. We've talked about some environmental issues and before we go to the controversy, I'll just mention diet because I appreciate the comment. So, I have thoughts on this. I'm curious about yours. Are there diets that make somebody more prone to autoimmune disease or inflammation in the setting of autoimmune disease?

[00:15:51] **Dr. Michael Levy:** I haven't seen any, I'm curious to hear your experience.

[00:15:54] **Dr. Benjamin Greenberg:** So, it turns out barbecue is protective again. I mean, it's really phenomenal but it's certain barbecue and so it's only Texas, North Carolina doesn't. So, in the world of MS and in the world of lupus and a little bit of rheumatoid arthritis, there's been evidence looking at high salt, high fat diets leading to increased markers of inflammation in the body. There's literature looking at things like Mediterranean diet and other things having lower rates.

[00:16:28] These are all what I would call loose association studies. And one of the things we talk about in our clinic is, does diet make a difference relative to autoimmune disease? In my opinion, the answer is 100%, yes. Do I know which diet each person should eat? 100%, no. Because it's going to be different for each person. There's a lot of evidence coming out in the world around the role of your microbiome, the bacteria that live in your gut as a way to modify your immune system. And there was a study done here at UT and at children's which really put this together in a nice way.

[00:17:06] And it looked at children who were getting bone marrow transplants for cancer. And so, these are kids with Leukaemia and they need a new bone marrow. And when we wipe out a child or adult's bone marrow and give you a new one, we're essentially getting rid of your immune system and giving you a new immune system. So, it's a great place to look for immune system diseases. And one of the dreaded complications in a bone marrow transplant is something called graft versus host disease which is I give you a new bone marrow and then that bone marrow starts attacking your organs.

[00:17:38] Now, it's not an autoimmune disorder because it wasn't your bone marrow. It was somebody else's. So, it gets its own name, graft versus host disease. And it turned out depending on which antibiotic children were exposed to in the weeks before their transplant changed the risk of graft versus host disease by tenfold. And they went back and they looked at stool specimens and found that as you changed the bacteria colonization in our guts, because we all have thousands of species of bacteria. If you change the bacteria in certain ways, your risk of graft versus host went up tenfold.

[00:18:14] That the antibiotic was selecting out certain bacteria that was protected against graft versus host disease. There's a huge interplay between the bacteria that live in our gut and what our immune system does. Other than taking an antibiotic, the only ways we know that you can modify those bacteria are by your diet by what you eat. Is there going to be a diet that's useful? Yes. Is it going to be useful for each person? No.

[00:18:44] As you read on Facebook, you absolutely have to do the gluten free Kosher vegan paleo diet and that's the way to cure everything. It might be for that person a life changing diet. It doesn't mean it's going to be life changing for everybody. We do in our clinic definitely recommend the exploration for each individual of the association between diet and how you feel and how you function. It's worthy of thinking about in all of our own minds.

[00:19:15] All right, so I'm saving the best one not quite for last, but close to last. I read on Facebook. For the record, I'm not on Facebook, I don't have an account. I've never had an account. I have to look over people's shoulders. Michael is on Facebook, I'm not. And somebody was showing me on Facebook maybe it was Trisha. She was showing me all these posts about how the Sooners were going to get crushed by the Longhorns. And then right after that, questions about the association between vaccination and autoimmune disorder.

[00:19:52] So, is that a question that's come up for anybody here? No. Oh, we can move on. So, there are two parts to the question about vaccinations and autoimmune disorders. I'll let you pick which one you want to take. So, the first is on causation, is there an association between receiving a vaccine and it causing an autoimmune disorder? And the second is safety of vaccinations once somebody has been diagnosed. So, dealer's choice, you can pick whichever one you want.

[00:20:21] **Dr. Michael Levy:** I'll take the first one.

[00:20:24] **Dr. Benjamin Greenberg:** Okay, go ahead.

[00:20:24] **Dr. Michael Levy:** So, first I'll say that I am on Facebook but my kids think that I'm old for being on Facebook. They're only on TikTok and they're like, only old people go on Facebook. So, yeah.

[00:20:33] **Dr. Benjamin Greenberg:** I never disagree with your children.

[00:20:36] **Dr. Michael Levy:** And then I think there's the middle generation. They're on the gram, Instagram.

[00:20:40] **Dr. Benjamin Greenberg:** The gram?

[00:20:41] **Dr. Michael Levy:** The gram or IG or whatever they call it now. Vaccinations. We looked into this early on because we did have quite a few patients who had a vaccine and then developed NMO shortly after. And it's really hard to not see that chronology because if somebody's been perfectly healthy all their lives and then they get a vaccine and then something immunological happens within two, three weeks after that, it's really hard to just wave that away. Oh, no, don't worry about that. But we put the data together in a blinded way where we said, let's take all of our NMO patients, line up all of their relapses with all of their vaccine history.

[00:21:23] And statistically, there was a small link. It seemed that people who had a vaccine while they were diagnosed with NMO had a higher risk of relapsing. And it wasn't a specific vaccine, it was all of them flu and Tdap and turns out the stronger the vaccine, the more likely the chance of a relapse. And I think the way that this makes sense to me is that the vaccines just stimulate the immune system just like any infection could have. So, a lot of people will tell me that they had COVID or that they had a previous infection before

they were NMO as well. And it's not which infection matters, it's when it happens. So, it's like the disease is there and then you take gasoline, you pour it on a fire, it just activates everything.

[00:22:12] So, it's not a specific infection or a specific vaccination. It's just immunological activation in general. And that may be how the gut microbiome works. If you could figure out how to get your immune system to calm down with a diet because you eat something and then the immune system is happy with whatever product the bacteria are producing, that may be another good way to do this is just use your diet to keep your immune system calm. But I'll take the second question just to say that vaccines can also be protective.

[00:22:42] If you have a disease where you're on a medication to prevent a relapse, it usually keeps the lid on your immune system and then you can take a vaccine and you can be sure that you won't relapse because the medication is keeping the immune system calm. And then you have the protection against that infection. So, then we looked at all of our NMO patients after they started a medicine and the ones who were vaccinated had a lower risk of relapse because the medication prevented the reaction to the vaccine. And then the vaccine prevented the infection, which can also trigger relapses.

[00:23:21] **Dr. Benjamin Greenberg:** Yeah, so along those lines in our clinic for our patients, a pretty blanket recommendation is even once you're diagnosed with filling your alphabet. So, whichever letters apply to stay up to date with vaccinations. This comes up a lot in our children's clinic where there's obviously a lot more vaccinations occurring. And we get asked in the setting of acute flaccid myelitis, for example, and we haven't had a single vaccine related recurrence in acute flaccid myelitis. If I think about my patients who had idiopathic transverse myelitis, I haven't seen a single case.

[00:23:55] I'm 20 years in now and I haven't seen a single case of a recurrence after a vaccination. And so, what I have seen are my patients getting ill with vaccine preventable conditions like influenza and stuff like that. And so, this remains a controversial area but if you look throughout autoimmune disorders and the risk of vaccinations and health, the data overwhelmingly supports the vaccination side of things. And this has been done in more common disorders like multiple sclerosis where they took literally thousands of people and half got that flu vaccine, half didn't.

[00:24:32] And there were relapses after flu vaccine in people with MS. There were more relapses in the people who didn't get the vaccine. And so, just because an event happens, it sequentially doesn't always mean cause and effect. So, it leads to a lot of consternation, understandably for everybody. So, with that, I want to leave some time for questions around these issues, around triggers relative to these autoimmune disorders.

[00:25:00] And no topic is too controversial for Dr. Levy. Ask him whatever you want but, yeah, so I'm not on the gram or Facebook, but my Myspace page is up to date. You guys can see me on Myspace. Everyone who laughed you just dated yourself. There's a kid in the back going, what's Myspace? All right, so any questions?

[00:25:27] **Audience Member 7:** What is that Texas barbecue that's the best barbecue?

[00:25:29] **Dr. Benjamin Greenberg:** Oh, so, the honest answer is it depends on which part of what animal are you eating. So, as a holistic, I lean towards Salt Lick barbecue in Driftwood, Texas outside Austin. That's probably at my top but there's a Lockhart Barbecue on the street that's not bad.

[00:25:51] **Audience Member 8:** Dr. Levy, you indicated two different studies that involved where patients were on immune suppressing medication. If a patient is not on immune suppressing medication, is there any data indicating the event of relapse following a vaccine?



[00:26:12] **Dr. Michael Levy:** It depends on the disorder. Are we talking about NMO? That's where we have the most data on this.

[00:26:18] **Audience Member 8:** The one that's relevant to me is MOG.

[00:26:20] **Dr. Michael Levy:** MOG, we haven't done enough studies in MOG because one of the problems with MOG and studying MOG is that a lot of people just get over it. The MOG goes away over time, especially in kids. So, they might test positive when they have their first event, might even have a second event. But then over years, it might just go away. And so then the question is, well, what if they get a vaccine a few years later? Is there a risk of a trigger relapse? We just don't know. The MOG antibody test has only been available in the US for six years. We don't really have enough data to answer that.

[00:26:53] **Dr. Benjamin Greenberg:** I'll just say anecdotally in our clinic and it's a mix of kids and adults. We haven't seen relapses anecdotally following vaccination. And then the second thing is I don't see Gigi in the room. I know she's here. But Gigi took the lead on a survey study through the SRNA and we got close to 500 individuals about different aspects of their diagnosis and relapses. And embedded in the survey were questions specifically about vaccination.

[00:27:21] And when we looked at it, we didn't see a signal relative to once you have been diagnosed relapses after vaccines. It's not a perfect study. This will be a plug if you ever do get links for surveys from the SRNA. I know everybody's busy and your email is full and all those things, it is actually incredibly useful data for us. And so, driving those response numbers up makes a big difference to getting at some of these questions.

[00:27:51] **Audience Member 9:** Yeah, you forgot to mention that we are in the Amazon age also, you know, social media, whatever. Is there any real immune system booster in the market? Because they announce, you know, everything. Is there a real one?

[00:28:11] **Dr. Benjamin Greenberg:** I'm glad you asked that question. This is something near and dear to my heart. So, for those of you with autoimmune disorders, the last thing you want is an immune system booster. So, in autoimmune disorders, the problem isn't a lack of function of the immune system, the immune system is perfectly fine. It's there's a rogue element that is confused and the last thing we want to do is boost them and give them fuel. So, we get this question all the time. People come in and say I'm on high doses of vitamin C and vitamin E and I'm taking -- my cousin sent me this immune booster that's made of elk brain and all sorts of things.

[00:28:54] Echinacea and every and I'm like, well that's great, but you don't want to do that. And so what we're looking to do. The way to conceptualize it is your immune system is a huge population of cells. Billions of cells. I only have 10 fingers. So, if you imagine you have 10 immune cells, you know, you have a flu cell, you got a COVID cell, a strep throat cell and all the different infections. And then you've got this one minority confused cell here.

[00:29:20] All these other cells are perfectly fine. What we'd love to do is just get rid of this cell and leave everything else intact. Unfortunately, our therapies today are a little broader. What we do is we get rid of, you know, these cells in order to get rid of that one confused. So, we actually ask people to stay away from immune boosters because the last thing we want is that thumb getting bigger.

[00:29:27] **Audience Member 10:** Is there any data to say that the area you live in has an effect like other than this nice moderate climate in California moved to the middle of a farm in Tennessee. Well, from that point on, I was just like always sick and I was very nice and calm over here. Is that documented? Is that a possibility?



[00:30:14] **Dr. Benjamin Greenberg:** So, there's old studies on where you grew up. Well, again, a lot of this data comes from multiple sclerosis in our world because it's such a much more prevalent disorder. And if you go back 70 years now, there was the beginning of literature that said where you grew up until the age of 15 dictated your risk of developing multiple sclerosis and the further away from the equator you were the higher your risk of multiple sclerosis. So, they draw these maps of the US. And Minnesota had large MS populations per capita compared to Houston and Dallas.

[00:30:51] And in the end, that risk was probably mediated by vitamin D levels through teenage years. The less sun exposure you had, the lower your vitamin D and Epstein-Barr that we talked about with multiple sclerosis. Remember I said it doesn't matter if you get it because everybody gets it, it's when you get it, it's your age and were you vitamin D deficient when you got exposed that implicates how the immune system handles it. So, the only studies I'm familiar with, with autoimmune disease and where you live are those studies.

[00:31:23] Now, what's interesting is that gradient has broken down and the risk is you get to 2023. The risk in Dallas and Houston is basically the same as Minnesota because none of us are getting vitamin D activation, the way we used to. So, every decade that difference has gotten less and less and less. Other than that, I don't know of a specific, I mean, you know, we can blame a lot of things on Mississippi if you want but I don't know of a specific geography.

[00:31:58] **Audience Member 11:** So, one of the questions I receive quite a bit is will this happen to my brother or sister? And if I have children in the future, will I pass it on to them?

[00:32:13] **Dr. Michael Levy:** I would say that for most conditions, the answer is probably no for all of the conditions that are managed here, especially MOG if there are any families out there with two or more members, I'd be very interested to study you because I've never seen that yet. NMO a little bit more common. I think there are a few patient families around and there might be some genetic predisposition there a little bit. Transverse myelitis very rare. We found a few people and learned a lot from their genetics about transverse myelitis, but that familial type is probably rare, probably less than 1 or 2%. So, for the most part, you can't blame your parents and you don't have to worry your kids.

[00:33:00] **Dr. Benjamin Greenberg:** Well, you can blame your parents for everything just for the record but yeah. Oh, sorry, let's go one then two.

[00:33:08] **Audience Member 12:** Just thank you on that first answer that you responded to about the supplements on -- what was the question again? He spoke of--

[00:33:23] **Dr. Michael Levy:** Immune boosting supplements.

[00:33:23] **Audience Member 12:** The immune boosters because that's a big one on us. Where we wonder if we should be boosting our immune system or not. And then my question is that, are there any supplements that we should be taking because we live in an era where there's just so many supplements that are being promoted left, right, and center, you know, especially also with vitamin D as well. You know, we are told that the one thing that will help us is vitamin D, we have to be constantly taking vitamin D to help us, you know, that is one thing that will help us to boost us as well.

[00:34:05] So, are there any other supplements that we should be taking? There's stem cells, there's this and that, you know, especially with like neurology issues that we are dealing with. Are there any supplements that we should be taking just to help us? And then another question is that we know that diet is a big deal and is there anything that we should do, are there any testing that we should do?

[00:34:32] Like, for example, I know there's genetic testing that one could do just to figure out what your makeup is. Are there any vitamins that you are lacking in as an individual, what your makeup is just to know what you need to eat more and what you need to eat less of? Is there any recommendation in terms of what testing you should do just to know what diets that would be recommended for you? Thank you.

[00:35:00] **Dr. Benjamin Greenberg:** So, on the vitamin side, so the reason Vitamin D is you'll hear about recommendations for Vitamin D3 specifically is there's evidence in a lot of disorders we're talking about. People with myelitis or at risk for neuromyelitis optica. A lot of literature on multiple sclerosis that says the risk of a relapse is associated with vitamin D deficiency. So, driving up vitamin D seems to prevent future attacks. These are largely uncontrolled studies. These are retrospective studies, but it's considered to be a very safe, very well tolerated supplement.

[00:35:37] And so, in our clinic, that tends to be a standard recommendation to take vitamin D3, to get levels up on blood work to between 50 and 100. I will caution everybody in the supplements world, even vitamin D3 it's a little bit like the wild west out there. So, there was one study, this goes back more than 10 years ago where they took 10 or 12 bottles of vitamin D3 off the shelf that all said 1000 international units on the bottle. On the low end, there was 50 on the high end there was 3 to 5000. There are no regulations on the manufacturing, there's no oversight on the manufacturing of supplements.

[00:36:14] In the world of things like CBD, we just had a talk from a colleague at Ohio State University who does a lot of work with CBD and epilepsy and they took 14, I think, CBD supplements off the shelf. In three to five of them, there was no CBD detectable. In three of them, there was THC at a higher rate than legally allowed. In four of them, there was arsenic at levels that is not considered safe. It is absolutely the Wild West and all these groups put very shiny labels on the bottle saying we certify organic and pure. They had arsenic in them.

[00:36:54] So, the issue with supplements isn't just which one and where's the sign? It's where you get the manufacturing and where you source it from and it's just, it's the wild west, it's a nightmare. But in our clinic, vitamin D3 is a standard recommendation and we try to do the best vetting we can around the sources of it. On the genetics and the diet side of things, I am not aware of any genetic testing that's been validated to tell us what to eat yet, relative to our disorders in terms of risk of new attacks. Are you aware of any?

[00:37:27] **Dr. Michael Levy:** I think it's a great idea if we could come up with that, but I don't know of any. I will add on the vitamin D story that we also used to tell all of our patients to take vitamin D. And then there was a big study, US government spent \$13 million to study vitamin D in MS. And they found that there was no difference. But what happened was they had two groups, they had the low dose group that took 600 units and then the high dose group that took more than I think 5000 units. And there was no difference in those two groups. The high vitamin D group didn't do any better.

[00:38:01] They were so convinced that it was unethical not to take vitamin D that they enforced that low dose group. They said you have to be on vitamin D. So, there was no real control group. So, we still recommend taking vitamin D. There seems to be very, very little harm. And the link epidemiologically is pretty strong and the harm is just not there. And I'll say that even when my wife was pregnant, they said, oh, you should take vitamin D3 for your baby. And pretty much in every context now, they'll say, well, you should take vitamin D3 and we have it in our house in the form of gummies my kids love. So, we still recommend it, but that's pretty much it, in terms of supplements.

[00:38:43] **Audience Member 13:** I recently went to my primary care physician and they said that they're recommending a hepatitis B vaccination. I'm on Rituxan and IVIG, is there any contraindication on which vaccinations should we stay away from?

[00:39:00] **Dr. Michael Levy:** You haven't been vaccinated already. A lot of people have already been vaccinated to hepatitis B.

[00:39:08] **Audience Member 13:** I thought but they are recommending for everybody to just get a booster but I have not, but I've never been vaccinated. I started Rituxan 17 years ago before they started.

[00:39:22] **Dr. Benjamin Greenberg:** So, just as a general rule of thumb, if you're on an immunosuppressant, live vaccines are contraindicated but killed or conjugate vaccines or MRNA or protein vaccines are safe. Hepatitis B is in that category, it's not a live vaccine. So, it is considered safe in immunosuppression. One of the things for everyone to recognize if you're on an immunosuppressant, however, is while a killed or MRNA vaccine is safe, the efficacy is lower when you're on an immunosuppressant.

[00:39:55] So, if you're on any of these medications. I shouldn't say any, several of them, not 100% of them. So, just because if you're on Rituximab or Inebilizumab and you get your flu vaccine, which is safe to do and we recommend it, it may not work as well. So, you still have to be vigilant for signs of flu and if you get flu, contact your clinician so you can be treated with an anti-viral, but it is safe to do as long as it's not a live vaccine.

[00:40:24] **Audience Member 13:** Which ones are live?

[00:40:27] **Dr. Benjamin Greenberg:** So, it changes. So, my rule of thumb for everybody is before you get a vaccine the last question you should ask is, is this live or not. To make sure they confirm that it's not live. There's confusion in the world, for example flu vaccines, the shots are killed, the nasal mist is live. So, it's not just that you're getting a flu vaccine, it's which one. And in the world of evolving vaccines instead of, I would never want to give you a rule to follow and then the next year, a different version comes out. So, I tell all my patients just ask and they will look it up and confirm that it's not live.

[00:41:05] **Dr. Michael Levy:** Yellow fever. And then there's the oral polio vaccine they used to use that I got. I don't think they use that anymore. I just want to add with Rituximab that's a particular concern with hepatitis because if you use Rituximab, you're knocking out B cells and that's really critical to fighting off hepatitis. So, if they want you vaccinated, I think that's a good idea. Not that you're going to come into contact with Hepatitis B anytime soon.

[00:41:32] It could be sexually transmitted or blood products or something like that. And you're on IVIG so that has protective antibodies because it comes from other people who've already been vaccinated. So, you're probably okay but if they do, if you've never been vaccinated for HEP B and you are on Rituxan, then you should take the vaccine.

[00:41:53] **Dr. Benjamin Greenberg:** So, we'll do one more question.

[00:41:59] **Audience Member 14:** Is there a brand that you recommend for those of us who have to take it?

[00:42:06] **Dr. Benjamin Greenberg:** Dr. Greenberg's vitamin D. My website is WWW. There's a coupon out front. Yeah, so see me after I can tell you. So, we looked into doing a vitamin D3 study here 15 years ago and to prep for it, I read manufacturing reports on vitamin D. If anyone's having insomnia, see me after I can cure it. All you got to do is read one of these very dense things. There were a couple brands that publish their quality controls and I'm happy to tell you about them.

[00:42:37] I don't speak for them or consult with them. I've asked for kickbacks. They won't give me any but I can tell you the ones that we saw. But in general, what you want to see is that they had independent and

ongoing quality assurance, not just when they set up their manufacturing, but with batches that come down the line that they send it for quality checks because vitamin D3 is actually not easy to make consistently. One more, sorry, whatever Denise says, I do. That's the rule.

[00:43:11] **Audience Member 15:** Thank you. Someone mentioned a few minutes ago about their primary care physician. What we're finding, my husband has neurosarcoidosis induced transverse myelitis. That's what we've been told. What we're finding is he got shingles, "go to your primary care physician." The primary care physician has no idea what neurosarcoidosis is and has no idea what to do with that transverse myelitis. "Here take this." I don't know if he can take that. They don't know if he can take that. Nobody. In my experience, I've had difficulty trying to find somebody who can answer our questions when we have that. If he gets a urinary tract infection or something and they give him an antibiotic, I don't know if he can take that. They don't know.

[00:44:04] **Dr. Benjamin Greenberg:** Yeah, so I think there's two answers to that experience. So, one is in general, any medication, I'm going to make a statement, Michael, tell me if this is accurate. In general, any medication a primary care physician would routinely prescribe, will not cause any problems with these underlying disorders. So, I don't know if an antibiotic or an anti-viral or a blood pressure medicine or a cholesterol medicine, a routinely prescribed primary care drug. I can't think of one that would be a problem with our disorders.

[00:44:40] **Dr. Michael Levy:** That's probably true but a primary care doctor might be more willing to use steroids when it's not necessary or something like that.

[00:44:48] **Dr. Benjamin Greenberg:** Yeah, with the exception of steroids.

[00:45:00] **Audience Member 15:** [Inaudible]

[00:45:00] **Dr. Benjamin Greenberg:** Yeah, so that goes to the second answer which is managing a care team. And so, for primary care physicians, these are rare disorders. And I'm not sure how many of you have had the experience of going into a health care provider saying you have fill in the blank and you watch them Google, literally Google it. Well, that instills confidence, you know? All Harvard trained physicians, all of them and they're googling it. None of the UT docs have to Google it. But since we allow the Harvard trained physicians in Texas, we have to meet them halfway.

[00:45:34] And yeah, in all seriousness the key is the communication between who's ever the primary for managing the neurology or neuroimmunology issues. Whoever the prescriber is of an immunosuppressant need to have a working relationship with the primary care physician. There needs to be open lines of communication and somebody has to instigate it. Usually, we ask the primary care physician to contact us and they've got email and cell phones and paging numbers. And so, if there's a question, they have multiple avenues for just running something by us.

[00:46:12] **Dr. Michael Levy:** Yeah, I think that they want that reassurance from us and they send us quick messages and we'll just say yes or whatever, but I think they like that reassurance. So, if you can make that connection for them, I think it would be useful to the primary care doctor too.

[00:46:30] **Dr. Benjamin Greenberg:** Yeah, and I will say for any clinician who is against you getting a second opinion or against connecting with another care team member, that's your red flag that you need to find another practitioner. So, if anyone ever says, "I can't do that" or "won't do that", say "thank you very much" and then it's time to find somebody.