How do these two systems interact to lead to these disorders?

You can view this presentation at: youtu.be/3IwvWsHtg2c

Dr. Michael Levy: [00:00:04] Well, hello, everyone. And in this session, we're going to try to explain how the immune system that I described interacts with the nervous system that Dr. Greenberg described to cause disease. And I guess, I'll just start off by explaining that the brain and the spinal cord and the optic nerve are in a privileged area that are separate from the immune system. So not all parts of the immune system have access to the nervous system. So, we think that something special happens in these diseases whereby the immune system is alerted to specifically go into the nervous system and look for something or to cause trouble. I'll post two different models.

[00:00:52] One model is that the immune system is set up in the nervous system. And in that model multiple sclerosis is the perfect example whereby the immune system kind of lives in the nervous system, and then periodically causes demyelination, causes problems, but it lives in the nervous system. And then you can sample spinal fluid from the nervous system, and you can see that the MS is kind of always there in the form of oligoclonal bands. And then the other model is that the immune system, the problem lives peripherally, lives outside of the nervous system, maybe in a lymph node or maybe in some other organ, maybe the bone marrow. And then from there, it initiates an attack into the nervous system. Kind of think aquaporin-4 NMO lives that way because we can detect the aquaporin-4 antibody at much higher levels in the blood than we can in the spinal fluid. So, we think that it kind of lives outside of the nervous system and then periodically attacks. So, Dr. Greenberg, what do you think about these two systems? Do you have an alternative model?

Dr. Benjamin Greenberg: [00:01:56] Yeah. One of the things that we still haven't sorted out with all these conditions is the timeline of events for immune system confusion. And so, I appreciate the context you provide and agree with these competing notions of the geography, if you will, within the body of where the abnormal immune system is being harbored. We also don't know for certain where the immune system gets triggered to have its confusion. So, using your geographic model, in one scenario an immune system gets triggered to be confused peripherally, maybe in the gut, in the intestines in response to a bacteria, maybe in the bloodstream or the lungs in response to a respiratory infection, or you keep going from there. Or does the immune system get invited into the nervous system for some other reason and in the context get confused. Great example of that is evidence that individuals with a viral encephalitis, the immune system is going in to fight the viral encephalitis can subsequently have an autoimmune encephalitis.

[00:03:08] So we think the immune system was perfectly normal and it was going into an attack on a virus, but in the context of attacking that virus got confused and subsequently there was an autoimmune disease. So, the geography plays a role both in terms of the long-term of these conditions, but also the time course and where do they get confused. And these are some fundamentally unanswered questions in our field but are critically important to how we define avenues for treating or preventing these conditions. I'll add one more conundrum to this. This notion of geography, and I agree we lumped the central nervous system together, but you and I have seen patients over the years who each have a defined autoimmune disorder but a very different target of the attack.

[00:04:02] So great example would be anti-MOG associated disorder. We have young children presenting with diffuse inflammation in the brain, spinal cord, optic nerves, we get 8- to 12-year-olds where the most common presentation is optic neuritis or bilateral optic neuritis, and the brain and spinal cord may look okay. And then you get the teenage years and later, where the most common presentation is a spinal cord presentation of myelitis. Now, any age group can have any presentation, but it's interesting to note that all of these individuals with the exact same, as far as we can tell, autoimmune disease, have different parts of their nervous system being targeted. So, we still have a lot to learn about why does a certain area of the nervous system get targeted in a certain individual on a certain day. And what it screams is we're missing a piece of the puzzle. And whether that piece of the puzzle is around the blood brain barrier relative to letting the immune system in or if there's something else going on, it's still unknown.

Dr. Michael Levy: [00:05:08] I would highlight that one of the new knowns is the target of the immune response at least in two diseases. NMO, neuromyelitis optica, where we know the target now is aquaporin-4 water channels, and MOG antibody disease, where the target is MOG protein. I would pose to you that at least now we have a sense of, since we know what the target is, now we can try to backtrack and say, "Okay, why is the immune system targeting those proteins? Why was it triggered in the first place? And then why, for example, in aquaporin-4, where aquaporin-4 is expressed everywhere, like lung and stomach, why is it that the immune response is only in the central nervous system?" So, I think we have new clues now that we can use to try to hone down on that pathogenesis, and hopefully one day target somewhere upstream so that we can stop the process before it even happens.

Dr. Benjamin Greenberg: [00:06:09] Yeah. I think part of... I think you're dead on that we now have paradigms we can test in different patient populations. But one of the things I caution myself, and my research team, and patients, and families about is there's a limit to the ability of certain things we can study. And one of the examples I point to that's been described for anti-NMDA encephalitis and anti-aquaporin-4 mediated neuromyelitis optica is there are at least a few cases reported, a couple of cases reported, where there seems to be a benign tumor, a teratoma that was a trigger very commonly associated with NMDA encephalitis. And these benign cellular growths can be microscopic. They're not a malignant neoplasm, and in fact, there's plenty of case literature to say that some individuals, the tissue grossly looks normal, in women it might be an ovarian teratoma. But then when you take it out, and on microscopic sectioning you find an area of cells that where the teratoma expressing the NMDA receptor or the aquaporin-4 receptor and eliciting an immune response. We can't go hunting with tissue for every microscopic growth.

[00:07:32] And so one of the things that is critically important is developing the other technologies, whether it's blood-based testing, looking for rare cells that are moving through the bloodstream, or cell free DNA moving through the bloodstream, or advanced imaging techniques. There are a lot of different tools we're going to use to try and sort this out. But at its core, and I'm going to make a shameless plug here on behalf of all the research teams in the world, yours, mine and everybody involved with the SRNA, when there are opportunities for our listeners, for our patients and our families to take part in research projects, if you're able and you're willing and it's not too much of a burden, look for the opportunities to share your data or share

a sample or have an MRI done. It's no fun, blood work is invasive, imaging takes time, but there is no way we are ever going to solve this in a dish or in a mouse model, all the avenues to sorting this out are going to move through partnering up with our community, and not just our patients but their families and friends. We need those controls; we need people to compare to.

[00:08:47] And lastly, I'll say on this point about research is this is one of the things that I really appreciate about the SRNA. The big tent approach to patient advocacy, having a community that has a diversity of underlying diagnoses, but at its core related to the talk I gave, the central nervous system being targeted, and the talk you gave, the immune system being involved in the pathology, allows us to compare and contrast these conditions. We've learned a lot about anti-MOG associated disorder by understanding anti-aquaporin-4 mediated neuromyelitis optica. And indeed, realizing that some treatments work better for one than for another, and that's giving us clues as to what's going on biologically. We would never understand that if we didn't have the diversity of patient populations taking part in the research studies that go on day in and day out,

Dr. Michael Levy: [00:09:44] Totally agree.

Dr. Benjamin Greenberg: [00:09:45] And so one of the things I would pose to you, Michael, is in my talk about the nervous system, I broke things down into two ways. I talked about the macroscopic view, the gross anatomy of an optic nerve, a brain, and a spinal cord. But we then zoomed into the microscopic view, the notion of a cell body, an axon, myelin that insulation. And we have classically, you and I were both taught, we just graduated medical school last week, we're very young, so we're very new at this. But we were both in lecture and taught that a lot of these diseases were demyelinating diseases, that the target was that myelin coating around the axon. And in fact, I still hear this left and right discussed with patients in the community. As you think about the immune system interaction, how important is it in your mind for us to actually redefine that correctly, because as we both know, there are mistakes in that categorization?

Dr. Michael Levy: [00:10:50] Well, I think that the way these things were originally defined was that people would die or they would get a biopsy, and you would look at it under a microscope. And if what they saw was the loss of myelin in 95% of patients, they would just say, "Okay, this is a demyelinating disorder and all these other people that have related disorders, we're going to call them all demyelinating disorders. And then we'll let you guys sort them out." I think a new or more modern approach is not to look at what parts of the brain are damaged, but to look at the immune system, and to see what parts of the immune system are activated and what they're activated against. Because I think when you look far upstream, rather than looking at the damage from the immune system. If you look upstream to figure out what triggered it and what they're reacting to, I think then you can be much more precise about defining the disease and then ultimately to treat it.

Dr. Benjamin Greenberg: [00:11:53] Yeah, there's beautiful work out of Alan Verkman and Jeff Bennett's labs on the aquaporin-4 pathology, and many others showing that this was an immune system not targeting myelin, but targeting astrocytes, primarily. And the damage to the myelin seemed to be a secondary event. So, there was demyelination, but that wasn't the primary pathology. And that makes me think about things from a neurology perspective very differently. And it explains why neuromyelitis optica is not multiple sclerosis or anti-MOG associated disorder. So, the target matters for a lot of different reasons. And as we get better at this matrix, what part of the nervous system is targeted at the cellular level, at the molecular level, and which part of the immune system is confused. That matrix will get us, I think, to much more specific categorizations of patients.

[00:12:52] And we've known for years, and you and I worked together in just the transverse myelitis world, and we've gotten so much better at separating out people who fit into the category of spinal cord inflammation

into their subsets based on which part of the immune system is confused. We practice neuroimmunology completely differently than we did 10, 20 years ago. And the more we chip away at this, about those two things, what parts attacked and by what, we're going to be far better at serving our patients and our families.