Neurosarcoidosis and Rare Neuroimmune Disorders

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[00:00:01] **Krissy Dilger:** Hello and welcome to the SRNA “Ask the Expert” podcast series. This podcast is titled “Neurosarcoidosis and Rare Neuroimmune Disorders.” My name is Krissy Dilger, and I moderated this podcast. SRNA is a nonprofit focused on support, education, and research of rare neuroimmune disorders. You can learn more about us on our website at wearesrna.org. Our 2023 “Ask the Expert” podcast series is sponsored in part by Amgen, Alexion, AstraZeneca Rare Disease, and UCB.

[00:00:40] For today's podcast, we are pleased to be joined by Dr. Giovanna Manzano. Dr. Manzano is a neuroimmunologist and a multiple sclerosis specialist and neurohospitalist at the Massachusetts General Hospital and the Brigham and Women's Hospital in Boston, Massachusetts. You can view her full bio in the podcast description. Welcome and thank you for joining me today. To start us off, can you just tell us what neurosarcoidosis is and how does it relate to and differ from sarcoidosis?

[00:01:19] **Dr. Giovanna Manzano:** Yeah, great question. Neurosarcoidosis is really just a fancy term that describes that sarcoidosis is now involving the brain. Sarcoidosis in general is a systemic rheumatologic disease, meaning it affects other organs of the body that are not the nervous system, most commonly the lungs. You find it in the lymph nodes, that's often how we get to biopsy evidence of the disease. Sometimes it can affect the heart. So, it is a really tricky condition because there are so many different ways that it can look in one given person depending on where it is. The neurosarcoidosis just implies that it has reached the nervous system, whether that's the brain, a cranial nerve, the spinal cord, or the peripheral nerves that we have. That's what that term refers to.

[00:02:05] **Krissy Dilger:** And what are the symptoms of neurosarcoidosis?

[00:02:11] **Dr. Giovanna Manzano:** The symptoms are really based on where it is. And I think that's what makes it challenging for providers as well as patients with this condition is figuring out the diagnosis. At first can be pretty tricky because it's not always the same set of symptoms that someone has. Really when I see a patient and this is their condition, what I ask them is any neurologic symptom and we dive into what that is to get a better sense. For example, if neurosarcoidosis is involving a certain part of the brain, let's say that's important for vision. If it affects the optic nerve, someone might have some vision loss. Whereas if it is more inherently in a peripheral nerve, whether that's the nervous system that is involved in how you sense or feel things someone might have numbness and tingling. So, it really just depends on where this condition is hitting in terms of how it will present.

[00:03:04] Most commonly, neurosarcoidosis tends to like the cranial nerves. A common one is the facial nerve and that's what it can give someone a Bell's palsy. Textbook education really focuses on, well, if someone has a Bell's palsy and then they have a Bell's palsy on the other side years later, neurosarcoidosis becomes on the forefront of a provider's mind and trying to figure out why that is because that's not so common

except for a neurosarcoidosis. There are some features that can help lead to the condition, but really, it's a combination of clinical symptoms, a neurologic exam and then diagnostic testing that ultimately leads you to that diagnosis and that are able to understand which symptoms are not associated with neurosarcoid.

[00:03:53] **Krissy Dilger:** Thank you. How is neurosarcoidosis diagnosed? And typically, who would be the physician or person diagnosing it?

[00:04:04] **Dr. Giovanna Manzano:** Yeah, great question. Because it is so elusive, once you dig into a particular symptom, the most common tests that we are going to use are primarily going to be neuroimaging. Things like a brain MRI and MRI of the spinal cord, potentially an EMG and these are all supportive to show that there is something inflammatory. Sometimes patients might need a lumbar puncture. That way we can look at their cerebral spinal fluid to look for any evidence of inflammation. But really, the diagnosis then comes down to whether or not you have biopsy evidence of the condition.

[00:04:41] This is where it's a little bit tricky for neurosarcoidosis. Because as you can imagine if it's involving certain regions of the brain, it may not be a possibility without a high risk of going in and actually getting a biopsy sample. The criteria that we use currently are based on a consensus group that was created from a team of expert neurologists and published in 2018. And what they defined as possible, probable, or definite are all different tiers of the diagnosis depending on where the pathology evidence is from a biopsy.

[00:05:15] To break that down a bit more, definite neurosarcoidosis means that there is evidence of biopsy confirmation of sarcoid in some nervous system tissue. Probable neurosarcoidosis means that you have biopsy evidence from a site outside of the nervous system, so outside of the brain, the spinal cord. But you have neurologic symptoms and all other causes have been already ruled out. And that's why it's probable because we don't have that brain tissue to fully say yes, sarcoid is in the brain, but everything else is excluded. And then possible just means that clinically the picture fits perfectly and beautifully and supportively there is evidence. Let's say there's a certain pattern on a brain MRI that a neurologist may notice, but there is no biopsy confirmation of sarcoid, whether in the nervous system or outside of the nervous system.

[00:06:08] Because of that, you often have a team of different types of doctors really looking to make this diagnosis. But primarily for neurosarcoidosis, it takes a neurologist and more specifically, oftentimes a neuroimmunology which is the field I practice in. We get referrals from primary care, but more often we're working with rheumatology because patients with neurosarcoid may have sarcoid elsewhere in their body first, which typically is filtered into a rheumatology domain. But I will say that sometimes this diagnosis is first made by a pulmonologist or a cardiologist depending on where the condition is. But then to get to the neurosarcoid piece, the patients will always be referred to a neuroimmunologist then to make that diagnosis.

[00:06:54] **Krissy Dilger:** That makes sense. And just a quick follow up, so you mentioned a rheumatologist. Can some of these symptoms mimic rheumatologic diseases such as rheumatoid arthritis and that thing?

[00:07:09] **Dr. Giovanna Manzano:** Yes. And that's really the sarcoid itself. Patients may have joint pain, they may have particular rashes. The most common rash is called erythema nodosum. And that's typically this red rash that's somewhat tender sometimes. And on the outside aspect of someone's shin usually is where it commonly is or uveitis, which looks like a reddening of the whites of someone eyes and a bit itchy and painful. So, these symptoms can be from a lot of different autoimmune conditions. It really takes a closer look by a specialist to figure out. Well, what's the cause? Is it something else autoimmune like lupus or is this sarcoid? And then from there, doing the rest of the neurologic workup.

[00:07:50] **Krissy Dilger:** That makes sense. I guess as another follow up to what you just said, how is neurosarcoidosis distinguished from other rare neuroimmune disorders such as acute disseminated encephalomyelitis, MOG antibody disease, neuromyelitis optica and transverse myelitis?

[00:08:12] **Dr. Giovanna Manzano:** I think the best way that I can conceptualize that is that neurosarcoidosis is unique and that it's more of an inflammatory condition rather than a demyelinating condition. That gets at the root of what's causing this condition versus the others that you mentioned. ADEM and MOGAD, and NMOSD, and transverse myelitis are all grouped under a family of demyelinating conditions whereas we don't think demyelination is what's going on in sarcoid. Rather, we see a dysregulation of some inflammatory cytokines and other formulations of something called a granuloma, which is thought to be this immune deposit mass lesion really. That on a pathophysiologic level, it's different, clinically, they can mimic each other. That's where it's tricky. And that's where getting a really good diagnostic tool such as a biopsy really helps to separate these things.

[00:09:08] And there are certain imaging features of each of these conditions that are a bit more telling [4, 1] versus neurosarcoid. For example, neurosarcoidosis likes to have a lot of what we call leptomeningeal enhancement meaning that the lining of the brain looks bright on our MRI with contrast whereas that's a little less typical of these more demyelinating conditions which like to affect the actual brain tissue. That being said, sarcoid can do that too. So, it really comes down to looking at someone's clinical course their imaging. But it's really the mechanism that's what separates them because clinically they can mimic one another.

[00:09:49] **Krissy Dilger:** And this is a related question, can someone have both neurosarcoidosis and a rare neuroimmune disorder or it's a one or the other type of thing?

[00:10:05] **Dr. Giovanna Manzano:** It's possible. I can't say that I see it often. There's one exception that comes to mind with you asking that question and it's that sometimes some of the medications that we use to treat sarcoidosis, so things that target the TNF-alpha cytokine in particular have been found to cause some demyelinating symptoms and lesions and even conditions in patients. You might have someone on an anti TNF-alpha medication that then develops optic neuritis or has lesions in the brain that look multiple sclerosis-like. In that way, it's not really that you then have both conditions, but you might think that this is a consequence of the treatment. That's on the whole quite rare. It's possible, I imagine, but we don't see that often.

[00:10:55] **Krissy Dilger:** We've hinted at the cause of neurosarcoidosis. But what is known about the cause of neurosarcoidosis? How do you determine the cause? And is there a genetic component?

[00:11:11] **Dr. Giovanna Manzano:** Great question. And I say we as in the field are always trying to actually answer that. I feel we're slowly getting closer, but because sarcoidosis presents in so many different ways and it's on the whole quite rare, it's hard to do really great studies looking at cause on a larger scale. But in terms of slow growth and development that we've had in this area, with these questions in mind, what we know is there's some dysregulation of the immune system, particularly that there's an increase of the cytokine TNF-alpha that you've heard me talk about a bit and there are different types of T cells. And so, there's one that's called the helper T cell. And there's a particular type, Type 1 that we think is implicated too.

[00:11:57] Generally speaking, we don't know exactly how or why or what goes wrong. But there is some immune dysregulation that makes those types of cells and cytokines more present and then they form what's called a granuloma. The buzzword on a biopsy is noncaseating granulomas that just describes the

way that the cells clump together. We know that we see that for sarcoidosis, that helps make the diagnosis, but we don't know yet what precedes it. There's a lot of hypotheses about could this be a reaction to some infection that someone had long ago? There is some research looking at patients who've had, for example, in sarcoidosis when it causes transverse myelitis, does it tend to happen at an area where there's some disc protrusion and some bony irritation to suggest that maybe there had to be some injury in the past that then this is a site where sarcoid forms? These are all hypotheses and at this moment in time, we really don't know why it is that someone develops neurosarcoidosis and someone doesn't. We don't have a great genetic underpinning yet identified.

[00:13:07] **Krissy Dilger:** Thank you. Well, it sounds like a lot of this is happening in the research realm to maybe give us some answers in the future. But, well, hopefully we'll have another podcast in five years where we'll know more. Getting into I guess who gets neurosarcoidosis, is it more common in a certain age, gender, etc.? Are there predispositions to getting this disorder?

[00:13:39] **Dr. Giovanna Manzano:** It's more common in your younger years. So, between the ages of 20s and 40s for someone to have sarcoidosis, which is pretty normal for most autoimmune conditions and some of the conditions you mentioned as well, the demyelinating diseases. Beyond that, it's really not a condition where it tends to affect one gender more than the other. Age is one thing. We also think about just demographics in terms of race. More often than not, those who are black can have sarcoid, but we see it just as commonly at times in Caucasians. I think that is starting to not play out as much as we thought historically. There's really not a great population assessment, but I would say more common for it to come around in the younger years although it is one of those things that can strike at any age.

[00:14:32] **Krissy Dilger:** Are there acute treatments for neurosarcoidosis? And if so, what are they?

[00:14:41] **Dr. Giovanna Manzano:** The treatment side of things, fortunately, we're getting pretty good at. Neurosarcoidosis has not yet had any defined clinical trials to really look at this in real time yet, but we are working on that. I personally am working on trying to design a few and pitch a few trials. We'd really like to be able to have more scientific data to support our treatments. But on the whole, we use steroids most commonly, sarcoidosis is unique in that it really responds very well to steroids almost too well because it can be very hard to wean someone off of steroids. Typically, if someone presents with a new flare or a new disease, we give them high dose IV steroids, we taper that off, but the taper is very slow. So, you're at least looking at three months if not six or more of being on steroids to just try to get things settled.

[00:15:34] Ideally, we have the sarcoidosis completely treated from the nervous system. There are instances where steroids alone are not going to be enough, or weaning won't be possible. If we get to that point where either the area where neurosarcoid is involved is concerning that steroids won't completely take away or we see that we can't wean off the steroids without the disease getting worse, we think about steroid sparing agents. And what I mean by that are other immune suppressants that are not steroids. Some common ones are mycophenolate, azathioprine, methotrexate. But really, we are finding more and more that the heavier medications such as Remicade, Infliximab. Those are very helpful because anything that targets the TNF-alpha is really getting at the root of the pathophysiology of the disease. Infliximab very much seems to be effective for all sorts of neurosarcoid types.

[00:16:34] And there is currently a project going on that I'm working on with a team of people to figure out what the consensus should be. When should we use these stronger agents? Should everyone get these upfront what is done now? But usually, we treat and then we watch how clinically someone does, how their

symptoms are responding and if they had imaging findings, how that looks with time and that's how we gauge how long someone's going to be on treatment and whether or not we need to escalate treatment or if we can keep on going with the plans.

[00:17:04] **Krissy Dilger:** And so, coming off of that, you mentioned flare. Is neurosarcoidosis considered a chronic disease? Can it be a one-time thing or is someone diagnosed for life?

[00:17:22] **Dr. Giovanna Manzano:** Great question. It is on the whole variable by person, but I would say is that it's definitely more correct to say it's chronic than not. Once it's there we can work to get rid of the neurosarcoidosis, but patients will be at risk of having relapsing disease. Historically, some of the epidemiologic studies that have been published will say that about two thirds of patients may just have a one-time monophasic event of neurosarcoid. That's great but that other third, relapsing conditions are very common, especially if it's an optic neuritis or a myelitis type.

[00:18:00] We also get this chronic progressive type of neurosarcoidosis and that tends to be the harder to treat brain lesions from the condition. The facial palsies and the cranial nerves, those may be more likely to be one time one and done, but you still always need surveillance because it is a tricky condition that could certainly come back. It's always hard to say you can completely cure it, but we at least like to strive for remission.

[00:18:31] **Krissy Dilger:** Thank you. So, what if any are the long-term effects or symptoms of neurosarcoidosis? Can it permanently damage organs or any things that people with this condition should be aware of going forward in life?

[00:18:51] **Dr. Giovanna Manzano:** I think it really depends on where the neurosarcoid effects. I'm going to use the word phenotype for that. If someone's first presentation with neurosarcoidosis was just cranial nerves. The facial nerve being the most common then with treatment that could recover, it could not recover fully just like a Bell's palsy from any other type. When you have something that has resulted in more of a mass lesion in the brain, that's a little tricky because it depends on how quickly someone gets to therapy, how effective the steroids are to melt it away or if they need to step up medication and where this actually was.

[00:19:33] What I've observed is patients who have what's called leptomeningeal disease. That lining of a brain or neurosarcoidosis actually in the brain tissue itself, there are not only structural changes that correspond with where the brain is affected. So, for example, if it's affecting a part of the brain that's really important for strength on one side of your body, we'd expect that to improve to a certain degree, maybe someone have some residual weakness or numbness, certainly possible, but I also even see the non-motor, non-sensory features. Sometimes some cognitive changes, especially with brain neurosarcoidosis involvement is that there may just be some difficulties with memory that we track, and we hope with immunosuppressive therapy, we'll get that back.

[00:20:21] But really partnering with excellent cognitive rehab therapists is such an important thing, making sure that patients stay stable in their general medical health and doing everything to just optimize their brain health moving forward in addition to treating the neurosarcoidosis is what we can do to really give the best outcomes. But if someone was concerned about any certain symptom they're noticing, it's definitely worth mentioning to your provider because the way that neurosarcoid presents to start may not be the only way it manifests. If you had a facial nerve once, but then now you're having new seizures, it might be related. Or if something more subtle, you are now having a little bit of blurriness of your vision and that wasn't the way your sarcoid was before, it's better just to mention it so it could be evaluated more fully.

[00:21:41] **Krissy Dilger:** That makes sense. You touched already on treatments for neurosarcoidosis. Is there ongoing treatment for someone with this condition in cases of continuous flares separate from the acute treatment?

[00:21:35] **Dr. Giovanna Manzano:** Mm-hmm. Basically, the way that we will decide together the patient and the provider is where the neurosarcoidosis affected someone and how they did with the first round of acute immunotherapy. If it was really hard to get off steroids and they relapsed or they never fully reached remission with steroids alone, then you're looking at being on maintenance therapy for some duration of time and then there's not a fixed two year, five year. It really just depends on someone how they recover clinically. And by imaging, there have been many patients that I've been able to not have to continue lifelong immunosuppressive therapy.

[00:22:15] It is very possible to need to have something more than steroids but yet not let that be a forever medication. And it's just dependent upon how hard and tricky it is to get rid of the sarcoidosis that is there. What this looks like again is we want to get patients off the steroids. Being on steroids too long has all sorts of side effects that many people are well aware of but just to say them, osteoporosis causes GI ulcers and reflux, and then you think about infections like rare infections that are less typical of the lungs and other places, so not a great forever drug even though it works so well. Then we think about things like mycophenolate, azathioprine, infliximab, and it might not be forever.

[00:23:05] **Krissy Dilger:** Well, thank you so much. That is the end of my questions, but I did want to just open it up to you if there's anything you wanted to add that we didn't touch base on or any closing thoughts.

[00:23:18] **Dr. Giovanna Manzano:** Well, thank you for having this topic on neurosarcoidosis. I think it is amongst many of the other rare conditions. One of the rare conditions that having more awareness of is so important for patients, for people in the community and for providers to recognize it because we'd like to think that the sooner someone's diagnosed and the sooner we get somebody treated appropriately, the better the long-term outcomes can be. So, it's a super tricky condition because it likes to masquerade in all sorts of ways and can be a little bit elusive when it comes to getting the diagnosis 100%.

[00:23:54] But once you make it, we do have a really good outline of how to approach neurosarcoidosis. But I think it's always good to just set expectations that because this is a condition that is so elusive and so hard to even diagnose that treating it does take time, but patients certainly should feel empowered to share with their providers if they're not noticing improvement because one it might be that the agent they're on is just not good enough for their sarcoid. The other side of the coin is that it does take a long time to recover from. Having both the patients, but also the self-advocacy to speak up and say that you're not noticing change is really important for making sure that you'll get the best outcome that you need.

[00:24:39] **Krissy Dilger:** Well, thank you so much. I think those are really important points for this condition and just in general good advice for patients when speaking to providers to just make sure to be as honest as possible and really advocate for yourself. Well, thank you so much for joining and hopefully we can continue this conversation in the future.

[00:25:01] **Dr. Giovanna Manzano:** Thank you for having me.

[00:25:05] **Krissy Dilger:** Thank you to our 2023 "Ask the Expert" podcast sponsors Amgen, Alexion, AstraZeneca Rare Disease, and UCB. Amgen is focused on the discovery, development, and commercialization of medicines that address critical needs for people impacted by rare autoimmune and severe inflammatory diseases. They

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