How do you get a diagnosis of ADEM, AFM, MOGAD, NMOSD, ON, and TM?

You can view this presentation at: youtu.be/WCdGRAfuHWw

[00:00:00] **GG deFiebre:** Hi, everyone. Thank you for joining us today for our first session. I am pleased to be joined by Dr. Kyle Blackburn, and so he's going to be giving a talk on how you get a diagnosis of ADEM, AFM, MOGAD, NMOSD, ON, and TM. And Dr. Blackburn is Assistant Professor in the Department of Neurology at UT Southwestern Medical Center. So, thank you so much for joining us, Kyle, or Dr. Blackburn, sorry. Let's see. And Valerie, I'm seeing about the captions. I will message you separately, Valerie, about the caption. So, Dr. Blackburn, do you mind just adding your slide?

[00:00:47] **Kyle Blackburn:** I am adding them right now, and can you see?

[00:00:54] **GG deFiebre:** We can, yep! All right. I'm going to just step away, but I will be here, so thank you.

[00:01:02] **Kyle Blackburn:** Excellent. Well, everyone, it's a pleasure. So, as she said, I'm Kyle Blackburn, and Ben Greenberg may be joining us here for a bit. But I was asked to give this talk today. It's something that I am really passionate about, is how we arrive at this diagnosis. So, I often see a lot of people after this diagnostic process has been going on for a while, and sometimes they still haven't established an official diagnosis. So, the parts of today, I'm hoping everyone comes away with an understanding of the medical lingo that we use and kind of just a basic understanding of why the terms are as they are. And then comes away understanding the diagnostic process and medicine in general. And then we're going to apply that process to these different disorders and show you how a diagnosis may change over time and how we may refine it.

[00:01:58] So, we're going to get into it, and I am moving. There we go. So, like I said, we're going to start first with learning the lingo, and these are the things that doctors use to communicate in medical records and in journals. And you may hear these words as well, and you may be infinitely familiar with them as well. So, this is the central nervous system, this very sophisticated drawing here. It is comprised of three different areas that we're going to focus on: the brain, the spinal cord, and the optic nerve that runs the eye. And when there's a problem with each of these, we'll kind of talk about how that's labeled. But we often refer to these terms in medical terms, typically derived from Latin.

[00:02:47] So, in Latin, brain becomes encephalo. The optic nerve, or the eye nerve, becomes optic neur. And the broad spinal cord term is myel, M, Y, E, L. And when somebody says something like, "A patient has

a myelopathy," that just roughly translates to a problem with the spinal cord, or an encephalopathy being a problem with the brain. It doesn't tell you any more than that. In the context of today, we're going to add an ending to those, itis, and that means inflammation.

[00:03:22] So, we're going to put these together, and any time that we're referring to inflammation of the spinal cord, it's going to be myelitis. If we're referring to the optic nerve, it's optic neuritis. And in the brain, it's encephalitis, and sometimes we combine these together. We'll show you that later ADEM. I always want to emphasize, these are descriptive terms. These do not explain why inflammation is going on. They are just a very rough explanation. They're just saying, "We're seeing some signs of inflammation, and it's in the optic nerve," for example. They do not show you, tell you why it's happening. That takes a little bit more detail, and we're going to get into that.

[00:04:05] So, anytime ... To kind of start here, the nervous system can be injured in a lot of different ways. You could have an infection. There could be a toxic exposure. There could be proteins building up, and nerves can be dying for that reason. Of course, many of us have heard of strokes or bleeds in the brain, but they can also happen in other parts. So, really, whenever a patient comes in with a complaint and we think it's a neurological problem, there's a long list of things running through our head. Whenever somebody comes to me having what we think is a spinal cord problem, a list of 50 or more things pops into my head on kind of my internal chalkboard, and then I have to use other things to narrow that down.

[00:04:47] So, already from the get-go, the list is extensive to the number of things that can happen, and our job is to narrow that down. And I show you that here on the right just from one of our leading journals, a list of possible things that can present with spinal cord injury, and this list is far from comprehensive.

[00:05:08] So, how do we get there? How do we go from all of these possible causes down to the main cause, or at least the working cause? Well, it's not unlike what you've probably seen if you've ever watched "House." It's a little bit more of a mental exercise. We may not be talking about it in real time, but this is ... It's a fairly good assessment of how we make these calls. So, we start by reviewing the symptoms and performing a neurological exam. This is to help us identify where in the nervous system the problem is occurring. That's something that we call localization in neurology.

[00:05:47] So, we're trying to pinpoint where the damage is occurring, because certain parts of the nervous system are injured by different things or more likely to be injured by one thing compared to the other. Sometimes, symptoms like weakness or pain or sensory loss, they can occur anywhere across the nervous system, and we're going to look for every possible clue that we can. But sometimes we keep the localization broad. We keep the number of possibilities broad so that we're not missing anything. And once we finally settle on one or two possible localizations, we'll start to formulate our list of possibilities, what we call a differential diagnosis, so these are all the possibilities that we think could be going on. And then we start trying to rank and file them. Well, what's most likely based upon the symptoms, the timing, based upon all of these other factors?

[00:06:40] We also start to do testing at this point. We'll start looking at imaging to confirm. Are we correct? Is this indeed a spinal cord problem? Oftentimes, when we're thinking of inflammation, we'll start getting spinal fluid analysis, so lumbar puncture, and we will also often obtain other blood tests, other spinal fluid tests and a series of other tests to try and narrow down these possibilities. And then, after all of that, we may have arrived at a diagnosis, or at the very least, establish what I call a working diagnosis. This is where we are still not 100 percent certain, but we have a strong possibility, but we are keeping other possibilities in mind because we have not had confirmation one way or the other.

[00:07:23] Now, I present this as a rather linear process, like this is an assembly line. This is actually very dynamic. This is constantly shifting based upon as new information, as it is gathered. So, you may be told that you have a diagnosis or at least a working diagnosis of spinal cord inflammation, and as we get more information, we may actually shift back to that differential diagnosis. We may look back and say, "Well, maybe this is actually a blood flow problem. Need to go reorder things and reconsider things." This can happen at any phase of the diagnostic process, and occasionally, it's necessary just to go back to the beginning.

[00:08:01] So, occasionally when things are really complicated or it seems like we're missing something, you just start from the top and go back through it again and collect information, and that's not unusual. So, as you can see, this process, because it's not linear, because it often takes time for us to get from Point A to Point B, to reach that final diagnosis, and sometimes there are nooks and crannies along the way, it can be confusing if you're on the other side of this. If you are in the hospital and you are not sleeping well and you are having a spinal cord event and you're being told a different diagnosis each day as testing comes back, it can be quite a topsy-turvy process.

[00:08:46] And it certainly... some people are left not really clear as to what their diagnosis is. So, I'm going to try as best as we can to explain to you how diagnoses are made and how and when those might change, but this is just to show you, this is not a straightforward process. It often requires a lot of thinking and rethinking at times to get to the accurate place. So, how a final diagnosis can be reached at the end of the day... rarely, all I need to do is a history and an exam, and a common example of that would be something like migraine. I can take a history, do a good neurological exam and reach the diagnosis without any other testing in most instances.

[00:09:28] But that's not true of the disorders we're talking about today. We often need other information to make the diagnosis, and imaging is often a crucial part of that. We're looking at certain patterns of imaging. We're looking at certain features on the imaging that help us decide, is this inflammation or not? And we'll get into some of that a little bit, but based upon certain patterns, we can make a diagnosis without any other information. And then, the last thing is testing which is things like the blood testing, the spinal fluid testing. I know a lot of people say, "I feel like I've had 10 ... all the blood drained out of my body during this evaluation process," because sometimes the testing is quite extensive, and it doesn't come back all at once. But those are the three facets.

[00:10:12] At any point, we may be able to make a final diagnosis or at least reach a possible diagnosis. So, to go over them quickly, what are the clues we use to determine if inflammation is in the nervous system? The first one, we look at imaging for several different characteristics, but one of the most common ones that we would use to see if there's active inflammation going on is contrast enhancement. So, if any of you have gotten an MRI for an inflammatory disorder, you have probably had an IV placed, and you were given contrast through the IV.

[00:10:48] And when that happened, what we're looking to see is, does any of that contrast leak into the nerve, the eye nerve, the optic nerve, the spinal cord, or the brain. If it's doing that, that's a clue that there's breakdown in the blood-brain barrier, which is a tight structure that's meant to keep things like contrast out of the brain. That indicates that there may be active inflammation in that area, especially if we're suspicious for an inflammatory disorder and definitely gives us the clue that there is active inflammation going on.

[00:11:23] And another important clue that we often look for is in the spinal fluid analysis. So, these are some of the tests we commonly get to look for signs of inflammation. Of course, inflammation involves blood cells, specifically white blood cells, so if we see a high number, we start thinking there's inflammation

there. We oftentimes see protein because, as I said, that blood-brain barrier is breached oftentimes in active inflammation, so we'll see high levels of protein in the spinal fluid. We look at sugar levels, and if they are dangerously low, we often think of infections, actually. But if they're normal, we still think about inflammation. And then we also look for antibody production, so antibodies are one of the ways your immune system refines and attacks foreign invaders. And if we see a high level of production of antibodies in the spinal fluid compared to the blood, that suggests that there's active inflammation going on in the spinal fluid, so these are also some of the other clues that we will be looking for.

[00:12:22] So, I'm going to take that information. You now know a little bit about how the diagnostic process works and how it's dynamic. You now know some of the clues that we're going to look for to assess for inflammation when we're assessing a patient for possible inflammation of the nervous system. Now, we're actually going to apply those details, and we're going to try and solve some cases, and we're going to kind of show you how the diagnoses are made and how they shift.

[00:12:52] So, we're going to start with spinal cord inflammation or myelitis. So, we're going to have our theoretical patient here, a 33-year-old woman who presents with leg weakness, sensory changes, and urinary incontinence that started 4 days ago. And I've switched from Dr. House to George Clooney in "ER" because Dr. House is kind of a jerk to patients, so I thought we'd go with someone that's a little more friendly. So, our patient presents to the emergency room, and Dr. Clooney does a full exam and history, and based upon that, makes a localization, and he settles that this is in the spinal cord.

[00:13:36] So, to evaluate that, he starts doing testing. We get imaging and spinal fluid analysis, and we see active inflammation in the spine as evidenced by this contrast enhancement. And in our spinal fluid, we see a bunch of white blood cells and elevated protein levels. So, there appears to be active inflammation in the spine. So, Dr. Clooney makes a conclusion that this patient has transverse myelitis. Well, that is a good working diagnosis. That is, as I've told you, that's a descriptive term. And in today's world, we certainly think that that needs further evaluation.

[00:14:19] So, at this point, we have some precursory information saying that there's inflammation in the spine. We have yet to figure out why. So, in this instance, more testing is needed to determine why spinal cord inflammation is occurring. Transverse myelitis in and of itself, without any other workup, is not an adequate diagnosis. So, we're going to go through a few scenarios with this case. So, we have identified spinal cord inflammation. Our working diagnosis is transverse myelitis, but we're doing more evaluations. And we decide to do a brain MRI, and we find that the brain imaging shows signs of multiple brain lesions.

[00:15:05] And based upon this information, based upon the pattern of the spinal cord inflammation and this pattern of the brain imaging, we can actually refine our diagnosis. We can go from having just vague spinal cord inflammation to actually having a specific disorder, and in this case, the disorder was multiple sclerosis. And this is actually a common scenario where someone comes in, they're having a spinal cord event. We see the inflammation in the spine, but then we also see evidence of either active or old inflammation in the brain, and that causes us to refine our diagnosis.

[00:15:39] So, already, you're seeing a working diagnosis can change as information is brought to the table. Multiple sclerosis requires treatment with immunotherapy, so it's actually a major game changer. We need to treat this to make sure that there is no active inflammation. And this may be true of certain patients that come in with initial spinal cord inflammation. So, as a patient comes in, a neurologist may decide there may be a risk for future events. We either need to follow you closely and see if you develop signs of multiple sclerosis, or we'll need to proceed with some other testing. So, occasionally, multiple sclerosis will be on the differential for someone that's just had a single episode of spinal cord inflammation, and they may need

follow-up to see if they ever meet the official diagnosis of multiple sclerosis. So, we're going to go through this case again, and we're going to kind of run this a few different times and show you a few nooks and crannies.

[00:16:38] So, again, working diagnosis of transverse myelitis. Patient has active spinal cord inflammation, but this time, we don't see any evidence of inflammation in the brain, so we can't make a diagnosis of multiple sclerosis, though we do see some inflammation in the spinal fluid. I just have the CSF empty this time. So, this person may be admitted. They've been told they have transverse myelitis. And then as testing rolls in, and sometimes this testing takes weeks, an aquaporin-4 antibody is found in the blood.

[00:17:12] And that is actually a scenario where the diagnosis changes. We refine our diagnosis. We go from just having transverse myelitis, a descriptive term, to having a secured diagnosis of NMO. So, whenever we see spinal cord inflammation and we find aquaporin-4 antibodies, we will oftentimes have to change that diagnosis, and this has implications for this person. We know that aquaporin-4 antibodies predict a high risk of having future inflammation in the nervous system somewhere, so this person would also be treated with immunotherapies.

[00:17:48] So, you're already seeing how a diagnosis can change based upon imaging or testing results, and it can change over the course of time. We're going to run through the same scenario again, and we're going to talk about the transverse myelitis. We have inflammation in the spine. The brain looks fairly clean, but this time, a week later, our MOG antibodies come back positive, and they're at a high level. And based upon the features, the diagnosis changes again. So, we go from a descriptive term like transverse myelitis to a MOG-associated disorder or MOGAD as we oftentimes refer to it these days. And this person may not need longer-term treatments other than what they need for their acute attack, but they're definitely going to need monitoring and making sure that they don't develop future attacks, at which point they may need treatment. So, again, we went from a descriptive diagnosis to a confirmed diagnosis based upon the results of testing. And we're going to run through another scenario.

[00:18:52] So, this last scenario, we, again, reached the spinal cord conclusion. We confirmed inflammation is going on, so we have a descriptive diagnosis of transverse myelitis, but all of the testing that we send back does not reveal a cause. So, at that point, we did not find aquaporin-4. We didn't find MOG. We tested for every infectious study that our hospital has available, but we found inflammation in the spinal cord with our CSF and our MRI of the spine. At that point, it is appropriate to label this case as what we call idiopathic transverse myelitis.

[00:19:32] And most people, when they are told by a doctor, or they are saying, "I have transverse myelitis," this is what they're referring to. They are referring to having idiopathic transverse myelitis. This means we have tested for every known cause that we think is possible, and we did not find a cause, so this case is defined as idiopathic. And I highlight that because this person should undergo monitoring. They should have to undergo symptom control to make sure that nothing else develops over time.

[00:20:08] But the diagnosis for the time being is idiopathic transverse myelitis. So, the teaching point here is once we've done all of our testing - and that may take a few weeks for everything to come back -, once that evaluation is done and we haven't found any sign of a cause for the inflammation, a patient may receive a diagnosis of an idiopathic disorder such as idiopathic transverse myelitis. This implies we didn't find a cause.

[00:20:37] And sometimes people are left a little bit confused by that, but we'll kind of talk through some of the situations where we need to change that diagnosis. And so, we're going to run through one more scenario for the spine. And we are going to determine that there's spinal cord inflammation going on. We did all of our testing, and everything is negative. Everything is normal. Our individual in this case is told they

have idiopathic transverse myelitis, and then a few weeks later, they come in, and they actually are confirmed to have an episode of optic neuritis. So, they went from having idiopathic TM to having a second event. They didn't have aquaporin-4 antibodies. They didn't have MOG antibodies, but they have had a recurrent episode. In certain situations, it is appropriate to change that diagnosis. Again, the diagnosis changes from idiopathic transverse myelitis to, in this case, you could make an argument for a seronegative NMOSD. And this patient may need treatments for this going forward. They may need specialty neurological care going forward because they have had multiple events.

[00:21:54] So, there are situations where NMOSD may be defined without aquaporin-4 antibodies, and that's the point here. Occasionally, a patient may be told they have idiopathic transverse myelitis, but that diagnosis could change as well. That's why the process ... It's important for this process to occur in close follow-up with a neurologist, especially if there are future events occurring. So, a diagnosis of seronegative NMO can be given if multiple episodes of inflammation are happening in different parts of the nervous system, but we don't find the antibody. So, idiopathic transverse myelitis can become seronegative NMOSD in certain circumstances.

[00:22:36] All right. So, I have kind of beaten the spinal cord train, beaten that path quite extensively and showed you some of the nooks and crannies. And we're going to talk a little bit about AFM in a second. But I'm going to take our transverse myelitis scenario, our myelitis scenario and flip it on its head and change it to a situation for someone that would typically have optic neuritis. So, these are symptoms of vision loss and pain that have been occurring for 4 days. And I just wanted to quickly show you that the diagnostic process is actually quite similar for these two disorders.

[00:23:09] So, aquaporin-4 and MOG antibodies and certain infections can both cause inflammation of the eye nerve or the spinal cord. So, as we walk through the diagnostic process, it actually looks quite similar. If we did extensive testing and this person did not have any known cause, we would label this as an idiopathic optic neuritis. Again, if we don't find a cause, it's labeled as idiopathic. If this person were to have future events, we may change the diagnosis to one of those recurrent disorders such as seronegative NMO, but the process is quite similar for optic neuritis.

[00:23:43] So, I wanted to kind of show that they're very similar, but I just used TM as the main example. And now we're going to run through a few of the other disorders and quickly talk about some of the considerations there. So, we're going to talk now about acute flaccid myelitis which tends to present a little bit differently than other causes of spinal cord inflammation. So, we have an 8-year-old boy who's presenting with fevers, a runny nose, and has developed left arm weakness. It's a little different than what we saw last time.

[00:24:18] So, our doctor may have to consider more than one localization in this case because there's more than one thing that can cause arm weakness but ultimately decides that they're going to consider spinal cord on the list. They obtain imaging, and they find inflammation in the spine, but they find it within the portions of the spine that hold the motor nerves. They do find signs of inflammation in the spinal fluid, but they also, because there was this fever and these respiratory symptoms, they test for enterovirus, and it comes back positive.

[00:24:53] This would allow this individual to qualify for a diagnosis of acute flaccid myelitis. So, this is a typical presentation for AFM, and in this case, we're using a lot of the clinical features and the imaging features to make that diagnosis. So, usually, a younger child having a fever with an upper respiratory illness that then develops weakness, commonly in the arms but can occur in the legs, with evidence of motor nerve damage in the spinal cord, that would qualify for a diagnosis of AFM. The flaccid part... I didn't cover this in our medical terminology course, but flaccid just means that the muscle tone has decreased and the arm is

floppier than it used to be. And this is typical AFM. And then the last disorder I'm going to kind of cover the ins and outs for today is ADEM. And I wanted to break this down, kind of what ADEM means. We already know the encephalo and the myelitis, but disseminated just means dispersed, and acute just means kind of fast in onset. So, I want to highlight, though the name is encephalomyelitis, you actually do not have to have spinal cord inflammation to have ADEM. It's actually kind of a misnomer in that way. But this disorder is implying that somebody has had the sudden onset of dispersed inflammation throughout the nervous system.

[00:26:26] So, they can have multiple areas in the brain. They can have spinal cord, and they can have optic nerve. So, they could have multiple areas hit at the same time. And this is more common in kids, so we're going to use another pediatric case. And this is a 6-year-old boy presenting with confusion, weakness, and a seizure. All of this seemed to have started 3 days ago. Last week, he had a few days of diarrhea and fever. So, we often hear with ADEM a history of some infectious exposure before the onset of these symptoms.

[00:26:56] And this is a little bit of a different scenario. We're dealing with the brain. We're not dealing with the spinal cord or the optic nerve, and there are many things that can cause brain inflammation. So, we have a young kid, and Dr. Clooney is in the ER. He has a kid with confusion and other features, and he doesn't reach ADEM right away. He actually decides to do a CSF analysis because meningitis is on this differential. And he sees inflammation in the spine and proceeds with a workup for possible meningitis. This diagnosis will be refined based upon the results of other testing.

[00:27:37] So, imaging comes back, and we can see inflammation throughout the brain. We may see evidence of it in the spinal cord and the optic nerve as well. As I said, those aren't required, but we certainly need to see evidence of dispersed inflammation in the brain. And that's how we refine this diagnosis, so a child coming in with confusion and after a recent illness maybe initially thought to have meningitis, and that may be refined to ADEM once imaging comes back. And the final diagnosis here was concluded to be ADEM.

[00:28:14] Now, there is one scenario where this diagnosis would change, and that is where MOG antibodies are found a few weeks later. And MOG antibodies are known to be a, so a cause of ADEM and may predict the risk of future events in the future. So, this case would actually be refined to be a MOG-associated ADEM or a MOG-associated disorder. We would want to follow this kid over time as well.

[00:28:39] So, I know that that was kind of a whirlwind. I'm certainly happy to answer any questions, but I wanted to cover some of the key points of this talk today. So, I want to highlight that terms such as transverse myelitis and ADEM, they are descriptive. We oftentimes mean idiopathic transverse myelitis or ADEM without a known cause. We have to do testing to determine why. We have to try and do digging based upon history and testing to figure out the definitive cause for these symptoms.

[00:29:20] People with inflammation in the nervous system may receive a more refined diagnosis based on the results of the imaging and the lab testing that they get. That's why things may change, what you are told may change one day to the next based, as more information is gathered. If, after a comprehensive evaluation, a clear cause for the inflammation is not identified, this can be labeled as an idiopathic case like idiopathic transverse myelitis. And in cases where recurrent episodes of inflammation occur, an idiopathic diagnosis may need to be re-evaluated, and that may need to be at an academic center with some expertise. And that's really the end of my talk today. I appreciate you all having me on, and I'm happy to take a few questions.

[00:30:09] **GG deFiebre:** Hi. Thank you so much for that, Dr. Blackburn. We did get a few questions. I thought it was a really great overview about very complex issue in terms of getting to a diagnosis. I know it can be challenging for folks to get to the right diagnosis and to go through all that process, so appreciate that. So, one question we got is, how common is it for the hospital team to miss a lesion in the spine or, I guess,

radiologist, potentially? They were initially told that their central nervous system was clean and that it was a problem with their nerve roots, and they switched neurologists 2 months later and then got a diagnosis of TM and that their lesion was quite small, apparently. Can you just talk a little bit about that?

[00:30:52] **Kyle Blackburn:** Yeah. It's a great question. So, spinal cord imaging is technically very challenging, and if it ... Even small movements can sometimes augment the testing. And I've had to run through this scenario just this week. I'm actually on hospital service myself, so I have had to very carefully look at a patient who had very clear evidence of spinal cord disease and look at their MRI very carefully to find the spot. So, if the area is small, it can absolutely be hard to detect.

[00:31:26] So, it's not unusual either in the clinic once somebody has come to us or even in the hospital for us to question our radiology colleagues if we're thinking that this MRI isn't normal because spinal cord imaging can be tough, and we have the information to say, "Something is going on in the spine, and we need to figure out what it is."

[00:31:47] **GG deFiebre:** Great. Thank you. And then, someone asked about sarcoidosis, that that can also potentially be [INDESTINCT] of longitudinally extensive transverse myelitis or LETM. Is that something that you've seen occur as well?

[00:32:01] **Kyle Blackburn:** That's a great question, and as I said, I didn't want to cover every possible cause of spinal cord inflammation. We would be here all day. And the asker of this question actually knows quite a bit. They're asking about longitudinally extensive TM. So, for everyone in the audience, that means whenever we look at some of these images, we see a long portion of the cord has been affected. And, yes, we have seen sarcoidosis hit the brain and the spinal cord. That has a little bit of a nuance to its diagnostic process, but absolutely, that can occur, and absolutely, it is treated as other causes of inflammation in the spine or TM. Yes.

[00:32:42] **GG deFiebre:** Okay, thank you. And so, you mentioned at the beginning about contrast enhancement being needed for some MRIs. So, is this necessary for kind of telling you the difference between active versus not active inflammation? And kind of when would you choose to do an MRI with contrast, if someone is experiencing relapse symptoms or for ongoing monitoring? Kind of, when do you decide to do one or the other?

[00:33:10] **Kyle Blackburn:** It's a good question, and I'll say practice has changed a little bit, meaning the way that we do things has changed a little bit in the last few years. So, not every active lesion will necessarily see contrast enhancement. For example, acute flaccid myelitis, we may not see enhancement. That's not unusual. And it's not impossible for us to not see enhancement if a lesion is really small or if we just, for some reason, did not, it just didn't have enhancement. So, if, really, the history tells us is this new or not new.

[00:33:42] Now, you're absolutely right. If someone is having symptoms of a relapse, we do like to add contrast. So, if we think someone is having a new event in the brain or the spine, we will often give contrast with an MRI. There are some people, and remember that scenario I ran through where the patient ultimately had multiple sclerosis. If we're doing routine monitoring of the brain, let's say, looking for signs of quiet inflammation, we don't necessarily need contrast because any MRI spot in the brain is going to clue us in that something is new, especially if we have a baseline before.

[00:34:19] So, if we're getting MRIs a couple times a year, and a new spot pops up, that indicates that there could be new inflammation. It does not mean that, it doesn't need to be recent. I may not give that person contrast because that involves an IV and adds a little bit of cost to it. But for more routine monitoring, we often won't add it. But for active, if we're concerned about an active relapse, we often do, yes.

[00:34:46] **GG deFiebre:** And then kind of related to the idea of imaging and all of that, we've sometimes gotten questions from people who have gone to different facilities to get an MRI, and they're told that the Tesla is different for each of the machines that they've been in. Do you mind just talking a little bit about that, and if someone's supposed to get an image done in a machine with a higher Tesla, like 3 Tesla?

[00:35:10] **Kyle Blackburn:** Yeah!

[00:35:10] **GG deFiebre:** Can you talk a little bit about that? Yeah.

[00:35:12] **Kyle Blackburn:** Yeah, so, Tesla. We're not talking about the car here. We're talking about the strength of the MRI magnet. So, there are... and there's a whole spectrum of them. So, occasionally, we will want a patient that has had maybe a 1.5 Tesla, which is a common scan out in the community, if we think that there may have been some smaller lesion that increasing the strength of the magnet may help us detect, we may ask them to get an MRI done on a 3 Tesla to see if, like I said, if they're coming in with signs of a spinal cord injury, per se, and that imaging is very challenging, maybe the strengthening of the magnet may help us detect a smaller lesion that was missed earlier. Occasionally, there are even stronger magnets that are primarily used for research purposes these days, but it's really just talking about the strength of the magnet. And the stronger the magnet, the more sensitively it may detect smaller lesions.

[00:36:12] **GG deFiebre:** And so, just to follow up to the person who asked initially about being told that their MRI didn't have anything unusual, they were told that there was an area of enhancement in the correct location that explained their symptoms, but the radiologist called it an artifact. So, can you just explain what an artifact is, if someone sees that technology being used in their MRI report?

[00:36:35] **Kyle Blackburn:** Right, so an artifact, we think of Indiana Jones and things like that. But an artifact on an image is basically, it's thought to be a false finding, in a way. So, if something moves, or if there's metal in the way of the magnet, it can obscure the signal or cause a signal to appear that may not actually be there in real life. So, common thing, many of us were kids, and we had braces. Braces are MRI-safe, but they obscure the picture. So, we see this kind of blob is the best way I can describe it, this dark blob, in parts of the brain if we get brain imaging in someone with braces, and that can cause an artifact.

[00:37:20] Occasionally, something may be called an artifact though that there may be a dispute about between the radiologist and the clinician seeing them. It's always important to remember, your radiologist is not actually examining you or talking with you, so if your physician, the neurologist, is seeing something, and they're like, "I don't think that this is an artifact," that is something to listen to because they're seeing your symptoms, and they are often going to be very sensitive to things that may be ignored otherwise.

[00:37:54] **GG deFiebre:** Thank you. And so then you also mentioned about spinal fluid, so if someone gets a lumbar puncture or spinal tap, how often is this fluid abnormal in, for example, idiopathic transverse myelitis? I know with MS, we talk about oligoclonal bands, and so with other conditions too, how often is it abnormal, is having a normal spinal fluid analysis considered, can someone not be diagnosed with TM, for example?

[00:38:24] **Kyle Blackburn:** Yeah. It's a good question. So, I always tell people, there are... Some of these tests are very, very what we call sensitive. They are very good at helping us get to the right diagnosis. They're highly sensitive and specific. They help us really drill in on the diagnosis. And an aquaporin-4 antibody is an example of that. The spinal fluid is... certainly, we like to see signs of inflammation, but not everyone has them. So, if we're seeing somebody later in their course, or if it's just very early even, sometimes the signs of spinal cord inflammation are very minimal to none.

[00:39:02] And it doesn't mean that they're not having spinal cord inflammation. So, like I said, there are some tests that are just very, very good at telling us inflammation is there, and there are some that are very supportive. But if they're negative, if those signs aren't there, we still have to look at the picture and make a judgement call. And if the story fits and suggests inflammation, and, for example, we see contrast enhancement on the MRI, we may say, "This looks like inflammation." So, I can't give you a firm number. It may be 60 to 70 percent of cases will have some sign of inflammation in the spinal fluid, but not all of them by any means.

[00:39:38] **GG deFiebre:** Got it. Thank you. And kind of, as we're getting to the end of our time, so you talked about the aquaporin-4 antibody and then the MOG antibody as well. Are these the only kind of two that can be confirmed with an antibody or biomarker kind of at this point in time? Are there potentially others out there that we just don't know yet?

[00:40:01] **Kyle Blackburn:** Well, now, that's a great question. There are some rarer causes that are associated with a biomarker. So, occasionally, we'll see a person have a very, very rare antibody that comes back. And, like I said, those are a handful of cases a year, and we're at a place that sees multiple people with transverse myelitis a week. So, rarely, we do detect other antibodies, not nearly with the frequency of MOG or aquaporin-4. It is also possible, and some people are speculating that there may be other biomarkers like that out there. What we call a biomarker, meaning these antibodies that really nail the diagnosis. So, there may be others out there. We just haven't... They haven't been classified yet. Sometimes that takes a while.

[00:40:51] **GG deFiebre:** And then, lastly you mentioned, when you were talking about AFM, you mentioned enterovirus. Are there other kind of viruses or any other sort of infectious agents that we think of that are associated with some of these conditions that kind of help pinpoint a diagnosis?

[00:41:06] **Kyle Blackburn:** There are. So, there are other infections. Sometimes the virus that causes the chicken pox can get in the spinal cord and cause inflammation. That's an example. And there are others as well that can do that. There's actually a whole host of them that is technically on the list, some more common than others. So, the infections sometimes can directly invade, and that's the case of enterovirus, this specific enterovirus. There are a whole host of those. But this specific enterovirus is actually thought to be invading the spinal cord and causing injury.

[00:41:41] So, there are some infections that do that. They get in the spinal cord and cause problems. There are also... Certain infections may actually trigger inflammation without being in the spine themselves, so we call that what we call a post-infectious disorder where you get this illness that is diarrheal, and it actually sometimes goes away. And then a week or two later, the inflammation happens. And it's thought that something on that infection triggered the immune response to the spinal cord and that that is related to the infection but not directly caused by the infection. The infection is not in the spine. It's outside of it, and the inflammation just moves there because it's confused.

[00:42:29] **GG deFiebre:** Thank you, and thank you so much for your time, Dr. Blackburn. We are at the end of our time. So, once we're done here, if everyone could just move back over to the stage next where you'll actually be hearing from me about the work that SRNA does. So, thank you so much for your time, Dr. Blackburn. Thank you, everyone, for joining us and listening today.

[00:42:51] **Kyle Blackburn:** Thank you all for coming. I really appreciate it.

[00:42:53] **GG deFiebre:** Thank you.