Unlocking the diagnostic odyssey

Understanding a diagnosis of ADEM, AFM, MOGAD, NMOSD, ON, and TM

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

[00:00:05] **Dr. Kyle Blackburn:** And I'm going to give a talk, that is a little more expansive than what I gave a few years ago about just how we reach these diagnoses and how we want people to reach these diagnoses and maybe provide a little bit of information about what we hope the future of these diagnoses are. So similar to last time, I always like to just start from the base so that everyone here understands the terminology that we use.

[00:00:32] Using medical lingo is one of the issues where people start running into trouble. So this is what we call the central nervous system and it consists of the brain and the spinal cord. And then for this purpose, we're also going to put in the nerve that controls vision, the optic nerve.

[00:00:50] So whenever we talk about the brain as an entity in medical terms, we tend to use the 'encephalo.' When we talk about the optic nerve, we'll see this optic nerve. And then a myelopathy or 'myel,' anytime we see that usually refers to the spinal cord for today's talk. And then we will add itis to it. And itis is a general term for inflammation. So putting it all together, if you have inflammation in your optic nerve, that is optic neuritis, if you have an inflammation in the spinal cord, that is sometimes called myelitis or also transverse myelitis, which we'll get into a little bit. And then if it's in the brain that is encephalitis.

[00:01:36] Now, I always want to emphasize these are descriptive terms. And if that's the one thing that you take away today, I wanted to be on Slide 2, you can go watch the Texas-OU game after this. So really these are descriptive terms but they are often used as diagnostic terms. And I'm going to try to relate to you the difference between a descriptive term and a diagnostic term. And that we shouldn't stop by just saying someone has transverse myelitis. And the primary reason for that is there are a lot of reasons why someone's nervous system can be injured.

[00:02:13] I'm about to be on service after this, I'm walking to the hospital, I don't get to watch Texas-OU in real-time. And I'm going to see a variety of things and just looking at the list of patients that I'm going to see, some of them have inflammatory disorders. But a number of them are going to have other causes for their neurological problem.

[00:02:31] And just to illustrate it, I know, I don't expect anyone to memorize the list on the right, but that is just a list from a popular review article or a review journal that we all look at in neurology that's just listing the causes of a chronic progressive spinal cord process. So you can see, it's not just as simple as just "transverse myelitis", there are many different causes of progressive neurological impairment.

[0:02:57] So in the next few slides, I'm going to walk through how clinicians start to think about inflammation in the nervous system. What are the clues that some of the clinicians will use to look through all of these possibilities and decide there's something inflammatory going on, whether it be an infection or an autoimmune disease?

[00:03:16] And the most important clue, even in today's world with all the technology we have is still a history. It's still something that we emphasize for neurology as a whole is that you have to learn to take a good history, because in many cases, that will still be the best way to make a diagnosis. And when it comes to diagnosing specifically things in the spinal cord, which is where I tend to lean a little bit, we really listen, we look for what we call the time to nadir. And that is the time that you reach the lowest point of the deficits. So we're really looking at how do things progress.

[00:03:47] I think we all know, for example, strokes are very rapid in onset and that tends to be true when they happen in the spinal cord as well. So if somebody has rapid deficits that happen rapidly, we start to worry that they had a stroke really until proven otherwise. And the inflammatory category can kind of expand a broader time frame, so somebody will often see their symptoms progress at least over several hours and often over several days if they're left untreated.

[00:04:17] Now, some people we identify very early. So certainly, if you go to the hospital and you're found to have inflammation within 12 hours, that would certainly not be you, we certainly don't think you may progress beyond that. But many of our infections and inflammatory diseases are going to be progressive over several hours or often several days if nothing is done.

[00:04:36] And then we have these more chronic processes. And there can be some inflammation in that bucket. I don't want to say that this is an absolute rule, there are exceptions to all of these. But whenever we get into things that are progressing over weeks to months and it's not due to somebody just having mobility impairments and being unable to becoming deconditioned because of that, we think about disorders like vitamin deficiencies or rare genetic causes or sometimes even cancer being associated with that.

[00:05:07] So this is really the crux and this is where you're going to find most neurologists should start figuring out how quickly did this progress. And sometimes people get a little bit annoyed whenever I'm talking to them in the clinic and they're like, well, I have these problems we need to talk about. And I'm like, no, no, no tell me how this all started. And that can sometimes take a while and you get into a lot of detail.

[00:05:30] The next clue, oftentimes after a history comes the work up. And I think many people who experienced that, somebody talked to you and then you started getting a bunch of tests and blood and get sat in hours in an MRI scanner. But the reason for that is inflammation in the nervous system often reveals itself, especially acute inflammation, we often look for signs on the MRI. And there are exceptions to every rule. Again, we're going to get into some of those, but inflammation often shows up as - acute inflammation will often enhance with contrast on an MRI.

[00:06:05] And this is again, there are exceptions to these rules that we can discuss and get into nuances. But for diseases like NMO, MOGAD, inflammatory myelitis, we often see contrast enhancement in the acute setting when they're active. And we use this to determine if someone having a new event, an old event. And

we'll talk about Dr. Tartar will later. A relapse versus a recurrence of the old symptoms, for example. So this is often a very powerful tool for us.

[00:06:33] And then the last tool that we often use when we're trying to confirm inflammation is the spinal fluid, the dreaded spinal tap. And these are the clues that we look for those elevated white blood cells, elevated protein levels in the blood, or in the spinal fluid, those can be seen for a lot of reasons. Glucose, we actually look at the sugar levels in blood and we expect those to be normal in most cases.

[00:06:56] And we actually have this test that often is associated with multiple sclerosis but it can be useful for a variety of conditions whenever we actually see antibodies being produced in the spinal fluid that aren't produced in the blood, implying there's a lot of active inflammation in the spinal fluid. So these are kind of the broad stroke tools that we have that would help us preliminarily say is there inflammation or not in the spinal cord history, imaging, and CSF? And those are often where the workup starts.

[00:07:27] So a lot of doctors grew up watching House, it's obviously a very controversial figure. But we often like to think of ourselves as sitting around and thinking about this. And sometimes we actually do pull out a chalkboard and draw things out if we're having really really tough cases. So it's not entirely untrue. But I don't walk around angry and cantankerous with people at all there.

[00:07:49] So this is the linear approach to how neurologists generally think. We take a history, we do an examination. And that information is used to say where a problem is happening in the nervous system, so we call that localization. And sometimes there's more than one, but sometimes we're able to arrive to a single place. We use that to formulate a possibility that list of injuries, the possibility that differential diagnosis. And then we use our spinal fluid and our testing, and imaging and then often a series of blood tests as well to try and figure out why this is happening.

[00:08:27] And then at that point, we try to reach a conclusion, at least a working diagnosis if not, at least a few possibilities that we still need to sort out. And a working diagnosis is something that can change. And I'm going to show you how a diagnosis can change as doctors get more information here in the slides that come.

[00:08:47] Now, I show this is a linear process that we're just going to reach a diagnosis using these new tools. The reality is it's a mess. So at any step along the way, doctors will often have to revisit a diagnosis based upon new information. For example, if someone has a recurrence of their symptoms have to leave the hospital, we now have to go back to the drawing board and figure out what's going on if that wasn't expected as part of their course.

[00:09:11] So it really just as - the thing that house gastritis sometimes the first diagnostic impression is wrong and we have to go back and rethink it again and again in some cases. And that can be very frustrating when you're going through that. But sometimes this information doesn't fold out in a neat pattern.

[00:09:31] So we're going to start with the spinal cord and we're going to go over the diagnostic process for what we're trying to move towards the term being myelitis. So there are a number of symptoms that lead someone to think of what we call myelopathy. So that's just a spinal cord injury of some sort. And those symptoms, I rank them in the three common symptoms being motor impairments, so some sort of weakness.

[00:10:00] Sometimes people can develop trouble with stiffness in a joint. Sensory symptoms like numbness, tingling or pain. Often those you may hear about the word a sensory level in people with spinal cord injuries. They develop a very very defined line where there's a loss of sensation. And then urinary and bowel issues. Usually, some incontinence or retention of urine or stool can also be a common sign.

[00:10:26] If we see multiple of those signs lining up together, a spinal cord injury starts to pop up on our list. Things like spasms, a sensation of tightness in the torso and sometimes even issues with heart rate or breathing and especially in certain causes of myelitis may also occur. So these are just some of the things that doctors are looking for as they do the history and exam to guide, we're in the spinal cord and we need to be looking in the spinal cord process.

[00:10:53] So we're going to talk a little bit about somebody coming to the hospital with this symptom. And in this case, we're going to have a 33-year-old woman presenting with leg weakness, sensory changes in urinary incontinence that's been developing over four days. And as you guys are already starting to learn, you're learning the terms and the profile something progressing over days, localizing the spinal cord myelitis is going to be very high on that list.

[00:11:17] So this is a common scenario that many people with transverse myelitis have gone through over the years. And we're going to switch to George Clooney now, I think he's maybe a better doctor figure. So you go through the history and the exam just as we said, doctors try to localize the lesion to the spinal cord. They start obtaining that imaging and spinal fluid testing, so the doctor says this is in the spinal cord. We obtain our work up, we see signs of inflammation. So we see contrast enhancement on that MRI that's this white stuff down here.

[00:11:52] And when we look in the spinal fluid, we see signs of inflammation. So we see an increased protein level, we see increased white blood cells. So the doctor says this is transverse myelitis. And I emphasize that this should be a working diagnosis, this should not be the final story. We've got more work to do as I think Stacy Clardy likes to say you have to earn a label like that and we need to do more testing to figure out why this is happening.

[00:12:20] But this is often where patients come to us. They say I have transverse myelitis and I say, well, let's look at what's been done to figure out why. And why is this happening? Why are we hitting that block and stopping at transverse myelitis and not moving on to the other tests? Well, some of it has to do with the fact that some of our testing, and I actually have the year on there this is 2002, not '22.

[00:12:44] But this is the criteria that we're using to diagnose idiopathic transverse myelitis in today's world. And I emphasize that a lot of these causes are still very important to us, we still test for them, there are so many clues. But the primary issue here is these criteria date back to 2002. So, for example, I show you this the common cell phone and the common way to listen to music in 2002 on the right.

[00:13:11] So we're using 2002 technology to diagnose things in 2023 and we're hoping to update that. But this is still technically the accepted criteria for how we should do things. Now, just like in today's world, we now have a device that merges seemingly all of our lives into one thing. We also have new technologies that are informing the way that we think about disorders like myelitis and optic neuritis.

[00:13:41] And so 2002, we didn't have aquaporin-4 MOG testing available. So those weren't recommended as part of the workup because they weren't part of it. They talk about the diagnosis of NMO because they recognize that as a disease state, but they didn't have a way of confirming it with a blood test as we do in many cases today.

[00:13:58] It really predates the recognition of enterovirus as a cause of acute flaccid myelitis and those outbreaks that we saw in the previous years. Over the years we've gotten better about MRIs and analysing them critically in people that have diseases like stroke of the spinal cord and sarcoidosis and fistulas. So we have better ways to diagnose those as well.

[00:14:19] I also want to emphasize that the 2002 criteria really said you have to have symptoms. They said they don't do symmetric, but you have symptoms on both sides of the body. And we now recognize that that's not the case. There are people that come to us with a single limb involved and they can still have a spinal cord inflammatory event. So these are just some of the several limitations to that criteria, but it's still the standard. So this is part of the reason why so many people with a myelitis event have trouble getting the diagnosis right the first time.

[00:14:55] So how should this conversation go in my mind? We localize the lesion as we do in neurology and say this is in the spinal cord. We identify that there's inflammation in the spinal cord using our tests. And then we can say that this - I'm going to say myelitis now, but some people may still use the word transverse myelitis that's still accepted.

[00:15:16] But instead of saying this is the diagnosis, the conversation should be, this is a group of disorders and we have some work to do to figure out why this is happening and that's where I emphasized. So just to give you - and I'm going to run through a few of these scenarios. Again, you guys are going to get bored with the slide, so just bear with me for a second.

[00:15:38] But one of the important things that we often do is whenever somebody has transverse myelitis - I want to run through a few of the common scenarios where that diagnosis can change. And again, I'm showing you this is a working diagnosis until we complete our workup. One of the common scenarios we see is somebody comes in, they have this inflammation in their spinal cord, and we start doing the full workup.

[00:16:00] For example, we obtain brain imaging and we see signs of inflammation in the brain as well, what we would technically call some encephalitis, but that term has other implications. But we see this in white matter inflammation in the brain and that often tells us that this has been going on repeatedly in the background. But this spinal cord inflammation was what brought it to this person's light. If it's characteristic, they will often receive a diagnosis of multiple sclerosis at that time.

[00:06:31] So this is where a diagnosis may change whenever doctors and healthcare professionals first have a working diagnosis or we do the work up, we revise our diagnosis. People with multiple sclerosis are at risk of having future attacks. Many of them need some treatment with an immunotherapy to prevent relapses. So learning point multiple sclerosis is a common cause of myelitis. So of the group of disorders, MS is one of the common ones. And it has certain characteristics on brain and spinal cord imaging that can give us a clue. So we can use the imaging itself to often make that diagnosis.

[00:17:09] And this is going to bounce around a little bit. So bear with me. We're going to quickly cover acute flaccid myelitis. So AFM, the way that we make this diagnosis though this is not absolute. It is often children though we have seen adults. An eight-year-old boy presents with fevers, a runny nose, so he has had some infection and then develops left arm weakness. So greatest asymmetry.

[00:17:33] Now, this can actually have more than one localization. So the neurologists and doctors have to be really really diligent to rule this out. But we eventually reached the conclusion this may be in the spinal cord. And our imaging actually demonstrates that in many cases. So we can see imaging in a specific pattern. In this case, I know that you may not be able to see this, but it's involving the cells where the motor nerves in the spinal cord live.

[00:18:01] And we may see signs of inflammation, but one of the ways that we may confirm this diagnosis, if we catch it early is actually doing the testing for the enterovirus. And if that comes back positive, we can certainly feel very reassured. But even in the right scenario, we may still feel comfortable making this diagnosis. And

there are very well-delineated criteria for acute flaccid myelitis. So again, we're seeing a scenario where we find inflammation. And we actually have a test that supports it. And in this case, that's acute flaccid myelitis.

[00:18:35] So again, AFM often presents with a respiratory infection in the past. Often, it can be very mild but often there is some fever. This is followed by weakness which can be very asymmetric. It can occur in one arm or both arms or the legs. And it often has signs of decreased muscle tone and over time, those muscles may shrink down an atrophy. So we see changes in the motor nerves on imaging and we do the enterovirus testing which can help us feel a little bit more comfortable with that diagnosis.

[00:19:12] We're going to go through another similar scenario where we've gone through the spinal cord, we've localized the lesion, we've obtained our workup. We confirmed that there's an inflammation in the spinal cord. We've looked at the brain, there doesn't seem to be any inflammation there, there's no history of previous episodes. We've looked at the spinal fluid, there's inflammation there, but we don't find an infection in the spinal fluid or in the body that would suggest myelitis. We don't find any results on our antibody testing, which we'll talk about a little bit later.

[00:19:45] So we really didn't find any signs of inflammation or we didn't find a specific cause for this inflammation. This is where we get into the term idiopathic transverse myelitis or moving forward, probably idiopathic myelitis. So this is somebody who we did everything that we could to work it up but we did not find the cause. And that still occurs despite the fact that we're using -- even using 2023 technology, we still have a significant proportion of cases where at that first stab, the known cause was not identified.

[00:20:18] So even after a comprehensive evaluation, a patient may have an idiopathic disorder, no known cause was identified. And this is often what people mean when they say that they have a diagnosis of transverse myelitis that the doctors have not labelled them with another label. But again, I always emphasize transverse myelitis is a group of disorders, idiopathic myelitis is a diagnosis. Does that make sense?

[00:20:47] And why do I harp on this so much? Why does it matter if somebody is labelled as idiopathic myelitis? Well, because at several different groups and this has been part of our experience too, oftentimes, if someone comes to us with an idiopathic label, they're seeing us for "transverse myelitis," as we look through the data, we actually are able to identify a diagnosis. So the entire impetus of this talk is to show that in many patients diagnosed with transverse myelitis, idiopathic transverse myelitis, the diagnosis changes when they go to someone with a little bit of familiarity with the disease.

[00:21:26] They may still have inflammatory myelitis. Many of them are diagnosed with something on the multiple sclerosis spectrum or sarcoidosis or NMO after testing, but the idiopathic label is removed and a more accurate label is put on. And in some cases, they actually don't have inflammation at all and there's actually a different diagnosis found. And I'm going to show you some examples of that here where we see some of the things that mimic myelitis. And you'll have to maybe take my word for it a little bit.

[00:22:02] This first one is a patient of ours that had a dural AV fistula of the spinal cord. So that is a blood vessel entanglement that can slowly worsen over time and spread up the spinal cord. And the reason that they were thought to have transverse myelitis was they had that contrast enhancement I told you can be seen. But the thing that clued us in is that contrast enhancement was there for several years.

[00:22:26] That would either imply we didn't put out the inflammation, which is a little unusual, or something else is going on. As we dug further, we were able to find clues that this person had a blood vessel tangle in their spinal cord. Fixing that actually reduced all of this swelling in their cord and helped them maintain stability.

[00:22:44] Another common one is strokes of the spinal cord so that rapid onset of issues. Oftentimes if somebody comes in after several hours after a stroke, we know that there's going to be that contrast leaking through. So that's actually another common mimic that we see is people say there's contrast enhancement, there must be myelitis. But if you ask the person, they actually had a very rapid onset of their symptoms.

[00:23:10] And even just one of the most common things that we see happen to a spinal cord, compression of the spinal cord that can also mimic myelitis. So you can actually get some of that contrast dye leaking through. You can get features that make the spinal cord look swollen during that time. So there's a lot of things that can happen to the spinal cord, even common things can mimic myelitis. And we have to be very very careful about making these diagnoses.

[00:23:34] Fortunately, in today's world, we often have very good descriptions of how these things present when they mimic myelitis. So we're able to make these diagnoses a little more accurately, if you're able to notice. So this is what I have argued for whenever somebody is about to make a diagnosis like an idiopathic transverse myelitis. So we find the problem, we start working it up as myelitis. We've done all the work up that we feel comfortable with for inflammation.

[00:24:07] But before we say they have idiopathic transverse myelitis, we stop and we go a different way. And of course, the workup said that there was negative. So this would be idiopathic from the inflammatory standpoint, but we look at those mimics. So in the future, I'm hoping that we ask doctors to look for the mimics before they make that idiopathic label. So that way that we make sure we truly know that this is an idiopathic myelitis and not one of the common mimics. And that's really what we're trying to move towards is having people do that extra cognitive step.

[00:24:39] So I'm going to talk about optic neuritis a little bit. I don't see Peter screening here so I can get away with that. He would run circles around me if he saw this talk because I'm not going to focus on it as much. But optic neuritis often presents with vision loss. Usually, people say like a smudging or a clouding of their vision in the middle. There's often pain associated with it, people will notice colors look less bright, and again, it tends to have that progression over several hours to several days.

[00:25:10] And again, Peter would not be happy to see this, but I'm just going to run through it quickly and say a similar diagnostic thought process applies to the spinal cord as does the optic nerve. We localize the lesion, we do a similar workup, aquaporin-4 and MOG can cause optic neuritis as well as myelitis, MS similarly. So we do this full work up. There are some infections that we often test for as well. And after a comprehensive work, if you feel comfortable that there was indeed inflammation there, we call it idiopathic optic neuritis and we manage that differently.

[00:25:45] Optic neuritis has its own mimics. So I want to emphasize that quickly. So we have had many patients come to us with the label of optic neuritis that we have changed. And again, strokes can happen in the optic nerve. That's what this first long term here is, that's basically a stroke of the optic nerve. And then these are a couple of infections that we've seen.

[00:26:07] Occasionally, our eye technician will just come to me and say, hey, this is an optic neuritis. So you got a little more work to do. So even patients that were seen in our hospitals and treated as optic neuritis as we use more advanced technologies in the clinic, we may find that there's a much larger problem and these are some of the things that we've seen. We've actually seen something called cat-scratch disease, which is a bacterial infection that involves the optic nerve. Or we've seen the shingles virus, the chickenpox virus that can actually affect the eye in some cases.

[00:26:41] So those are just notes on optic neuritis. Now, I want to talk a little bit about NMO and then of course, MOG before we go into it and explain how we make those diagnoses and why it's important to distinguish those from somebody who has an idiopathic disorder. So again, we're not going to run through all of the details about NMO but this is a disease that can hit multiple parts of the nervous system, it can hit the brain, the spine or the eye nerve.

[00:27:05] And the big hallmark here is many of our patients with an idiopathic disorder, we think that their risk of relapse is overall low, but a person with NMO, especially if they have an aquaporin-4 antibody has a very very high risk of having a relapse and relapses of NMO can be very severe. So we have an opportunity to intervene. So this is definitely going to be an important step in the work up for myelitis or optic neuritis in the future is making sure you're testing for an aquaporin-4 antibody in most cases.

[00:27:34] And I emphasize, we've actually tried to make that very easy because NMO can be very severe. A single attack of myelitis plus an aquaporin-4 antibody buys you that diagnosis. So it's really important to test for. And then in the criteria for NMO they actually highlight some of the things and you'll see optic neuritis and myelitis listed as the top Number 1 and Number 2. But we like to emphasize that a number of things can happen and I'm going to show that to you later.

[00:28:04] So again, a patient can come to the hospital, have inflammation in their spinal fluid confirmed on their MRI with that contrast enhancement in their history and then we do this test for aquaporin-4, and that diagnosis changes. So you may be told, you have transverse myelitis. Again, the conversation should be, this is a group of disorders, not a formal diagnosis, we've got some work up to do. And in some cases, we're going to find that aquaporin-4 antibody. And in those cases, we actually revise our diagnosis to NMO and this is someone that probably needs treatment because of the risks.

[00:28:42] Now, we talk about NMO again as an optic nerve and a spinal cord disease. But this is a disease that can hit the brain. And this is often a step where sometimes people are not diagnosed in a timely fashion and we've seen people have multiple relapses before somebody finally realizes that they need to test for an aquaporin-4 antibody. And these are just some of the patients that I've seen in really a 4-5 year span of doing this independently that show some of the patients that I've had that came in with these "uncharacteristic, typical NMO lesions" that we wound up finding an aquaporin-4 antibody on and fortunately stopping this process.

[00:29:20] Now we're going to move on to something else about NMO, another caveat the diagnosis. So somebody comes in, they had a spinal cord event. We label them as having idiopathic transverse myelitis, for example, at that point, that's the working diagnosis. But a few weeks later, we did all the work up including the aquaporin-4 antibody, it's negative, but a few weeks later, they developed optic neuritis. There is a way to achieve a diagnosis of NMO without an aquaporin-4 antibody. It's important to acknowledge that not all parts of the world have this technology readily available though we hope someday to have methods for that to be available. So the diagnosis of NMO can be made purely based upon typical clinical features that distinguish it from multiple sclerosis. But in someone who's had multiple attacks signify that they need treatment.

[00:30:15] So a person can be diagnosed with what we call zero negative or in the world double negative NMO today because of the MOG antibody being a common thing. And that highlights this here. These patients have to have two characteristics in different parts of the nervous system and they have to have at least one of those core features. And either the testing is unavailable or the testing for aquaporin-4 was negative and it has to be done using reliable methods.

[00:30:42] Now, the last diagnosis I'm going to cover for the moment, we're going to move on in a little bit, but I want to talk about MOG antibody disease. One of our more recent additions to the SRNA is similar to

NMO. A certain percentage of MOGAD patients can have inflammation, it's most commonly in the optic nerve, but they may occur in the brain or the - I listed eye or optic nerve, I meant spinal cord optic nerve. So it may occur in any of those same three regions that NMO can occur or even MS can occur, but the difference here is there may be a significant proportion of people who have a single event. There's also a not insignificant proportion of people who may go on to have further events down the road.

[00:31:31] So we need to be following these patients closely. And we recently got criteria for what we now call MOGAD and I'm not going to run through them, but it essentially includes similarly to the NMO criteria, typical clinical features plus a positive antibody. So similarly, we do our work up, we find, let's say inflammation in the spinal cord, we do our test, we acknowledge it's a group of disorders. We do our test, we find a MOG antibody, and that if you're diagnosed with MOGAD at that point.

[00:32:03] And MOGAD, again as I emphasized, may not necessarily have another event down the road. So this individual would undergo close monitoring. And if they developed another event may need immunotherapy at that point. So I also want to emphasize that unlike an aquaporin-4 antibody, there are some issues with what we call the specificity of the MOG antibody. That means we can sometimes detect the MOG antibody in people that don't have MOGAD, they have very different features. For example, multiple sclerosis or about 1% of the people that have a neurological problem, though 1% of neurological disorders aren't MOGAD it's actually a much lower proportion. So in some cases, maybe the level of that antibody that we detect is significant. Although, I don't want to say that's an absolute rule either. So it takes feeling very comfortable with that diagnosis and using our criteria to make sure that we're accurate.

[00:33:02] And then we're going to move on to ADEM really quickly. So ADEM to cover it, it's got several of these words built into it for a reason. So it's acute, it's disseminated, which means it's dispersed throughout 'encephalo,' so the brain is involved and then myelitis. So it has spinal cord inflammation. They didn't want to add optic neuritis to it because then you're just going to have - they couldn't really come up with a clever acronym. They couldn't have - just added too much, but they can also have optic nerve involvement. So ADEM is a widespread diffuse condition that occurs all at the same time.

[00:33:33] And that can happen often more commonly in children. So this is a little bit unique in that patients with ADEM have what we call encephalopathy, which means they have some cognitive or loss of consciousness or impairment of their consciousness or awareness. They can be confused. So a six-year-old boy presenting with confusion, which is very different than we've talked about before.

[00:34:00] They can have seizures, so he actually had a seizure. We haven't talked about seizures yet. But also has some weakness that started three days ago. And oftentimes we associate this with a condition like a febrile illness and he had some diarrhea and fevers in the days prior to this happening. So the work-up confusion and seizures make neurologists ping that something's going on in the brain. So that's where we go first. In this case, we often we may rule out things like meningitis rapidly. So we get our spinal fluid right away and we find signs of inflammation.

[00:34:33] It's not unusual for people to be treated for infections at this time because meningitis is its own emergency that needs antibiotics. But as we get more information, we say, this doesn't look like meningitis, it looks like there's something widespread throughout the brain. And if they do other testing, they may find inflammation in the spinal cord or the optic nerve as well.

[00:34:56] So again, something that happened rapidly involves confusion spread out through the nervous system. We revise our diagnosis and say it's ADEM. Now to keep it brief here, a certain proportion of patients with ADEM will go on to have MOGAD, up to half of them actually, in some studies. So we can actually have

somebody presenting with ADEM test for the MOG antibody comes back positive and we give them a more accurate label.

[00:35:22] So you guys are now ready to go diagnose rare neuroimmune disorders, that's my goal today. We needed more doctors and now we've got them. You're getting a certificate on your way out that you can show. So the key points here, terms like transverse myelitis, ADEM, optic neuritis, these are descriptions. They are a working diagnosis, they are not a final diagnosis, you have to work through a process to figure out why.

[00:35:52] People with inflammation in the nervous system often receive a more refined diagnosis based on the results of imaging and tests. So you may be told you have optic neuritis, but the conversation should be very different. And I argue that to our clinicians, we need to be telling people this is a group of diseases and why. That communication matters. It's so that you can understand your condition better.

[00:36:15] If after a comprehensive evaluation, a clear cause for information is not identified, and we've ruled out mimics, I will add that in. The cause can be labelled as idiopathic in most cases, so we did not find a cause. In cases where recurrence happens, we need to revisit that, just like our patient that had a diagnosis of myelitis. And that was revised to NMO after they had a relapse.

[00:36:42] So in certain cases, we need to be re-evaluating our diagnosis and going back to the drawing board and we need to be transparent about that as doctors. And then when confronted with an idiopathic disorder, we have to do our work up for mimic and keep those in mind as well and not just shut off the cognitive process. That's all I've got for today. Happy to take a few questions. Please.

[00:37:14] **Audience Member 1:** [Inaudible]

[00:37:20] **Dr. Kyle Blackburn:** It's a fair question. So there's a couple ways that scoliosis can intersect. So some of our younger patients with AFM, for example, can develop scoliosis and need interventions for that as a sequela of having AFM. The scoliosis itself often isn't misdiagnosed as myelitis at least not in my experience. It's not one of the more common ones we would see. Saw some other hands go up. Sure.

[00:37:49] **Audience Member 2:** So you didn't talk very much about the nausea, vomiting, and things like that. I presented twice in the emergency room a couple of months before having neurological symptoms, but I was aware of it with that and they just didn't know to do with me. Is there anything that isn't happening that could happen? So where doctors know better, how to recognize that. Maybe order an MRI done or something.

[00:38:17] **Dr. Kyle Blackburn:** It's a really, really good question. So one thing we didn't cover and you're right, I didn't cover this is the diagnosis of NMO. NMO can occasionally hit the centers of the brainstem that are responsible for nausea and vomiting and occasional hiccups as well. And for some people that's the only symptom that they come with and they've had it for weeks. And we've been lucky enough to capture people at that point and treat them and they have no other relapses.

[00:38:45] But it's very very challenging. So, obviously, this is a very rare cause of nausea and vomiting and there are a lot of people who have unexplained nausea and vomiting out there. But we have made sure that the community is aware of this and definitely, if someone has any hinting towards a neurological sign or several days or weeks of nausea or vomiting, that hasn't gotten an MRI, I do think it's reasonable to do in that phase just to be certain. And we've certainly executed on that and select patients in the hospital. Please.

[00:39:20] **Audience Member 2:** [inaudible]

[00:39:34] **Dr. Kyle Blackburn:** Sure. I always tell people that rotate through my clinic, you're about to see several things you've never heard about and that's normal. Unfortunately, there is a need to go through - there probably is a need to do this and do better education of healthcare professionals in general so that they're aware of this. Absolutely. I agree with you.

[00:39:57] **Audience Member 3:** So it seems like we're trying to get rid of the word transverse and I was wondering if you could elaborate on that. And since we're all clinicians now, are we all going to be getting some CME and CEUs for that?

[00:40:17] **Dr. Kyle Blackburn:** I think you're already worried about maintenance of certification, so you're already a clinician. So the question was - and for some reason, this always falls on my head because I seem to be the one that brings it up, the dropping of the word transverse from diagnosis, a transverse myelitis. And I always explain, there's really - technically the term is inaccurate in today's world, and we can wax and wane about the history of this diagnosis.

[00:40:36] But we know that - when we say transverse that's often an anatomical plane in the spinal cord and we know that myelitis expands all spatial dimensions of the spinal cord. So it's a technically incomplete term in that manner. But one of the other reasons that I think that we need to update the terminology isn't just that, I mean, if we all accept that transverse myelitis is the term, there are plenty of inaccurate terms and just move on. But language does matter in some cases. And I feel like for so long now that diagnosis has just led to what I showed you that stop. It's, you have transverse myelitis and we're done.

[00:41:14] And as you see in today's world, we know enough that we can dig down in two-thirds of the cases and find the cause. So part of the case that I make for updating this to myelitis and I think other experts are adopting this term and putting it in the literature themselves. So it's already going, it's already catching catch contraction is that we're changing people's thought process. So if we have a new term or at least a revised term, we can say, well, what is myelitis? It's got several causes.

[00:41:45] And you can add that this person had MS-associated myelitis or AFM, which has myelitis in the word. So it allows for us to add on those adjectives to more accurately describe things. So I think it's really just a movement to make sure that you're getting the right diagnosis earlier.

[00:42:08] **Audience Member 4:** Thank you for that. So I am an NMO patient recently diagnosed and I just want to understand, I know that you explained it, but I want to understand it. Initially, I was told that I had optic neuritis and then I was told that I had NMO so I just want to understand what the relationship is between the two. Is optic neuritis like - I just want to understand what the relationship is between the two. So I'm just a little confused.

[00:42:47] **Dr. Kyle Blackburn:** Yeah. And I'm not surprised people are confused. We're teaching these things to our residents in a couple of months and I have 12 hours to do it there as opposed to 45 minutes. And this is more than enough time to go give an overview, but it is confusing for people. And we sometimes see people coming in saying, well, I'm a really rare person, I have transverse myelitis and NMO. And that's actually technically incorrect.

[00:43:11] So again, optic neuritis and transverse myelitis are descriptive. They are saying there's inflammation in the nerve of your eye. They should not be the diagnosis. If you had no known cause it should have been idiopathic optic neuritis. But really, what they should have said is we have a lot of work up pending here and we need to - one of those things would be the NMO test and when that came back, that's probably when

they revised that diagnosis. So you had a working diagnosis, they just didn't explain that. You have a working diagnosis we've got some work to do before we say that this is just without a cause or if we find a cause we have to revise. I think we got time for one more, maybe.

[00:43:59] **Audience Member 5:** You listed torso tightness as a rare symptom. Is there any understanding of what is causing that torso tightness?

[00:44:09] **Dr. Kyle Blackburn:** Maybe I may have spoken misspoken there. It's actually not rare, it's actually quite - I don't have an exact percentage in front of me, but it's probably at least half if not more of patients will report that feeling. So a tightness in the torso or the abdomen is often where people will say it feels like somebody has taken my belt and just tightened it too tight or I feel like there's a snake. Somebody used to love to call it the MS hug that we see in other diseases.

[00:44:33] So it's almost like something is hugging you and won't let go. I've heard a corset you hear all kinds of things like that. So it's not rare but it is a symptom that really makes neurologists scream spinal cord, oftentimes other doctors that don't see as much spinal cord injury as us will start to think about chest pain, which is totally reasonable because heart attacks, which are obviously something we need to be diagnosing can occur in this manner.

[00:45:03] **Audience Member 6:** What is the mechanism that is generating that?

[00:45:05] **Dr. Kyle Blackburn:** It's a good question. It seems to be some sensory issue. And we hear patients also describe a feeling of tightness in the leg. So I think it's something akin to that. Sometimes it seems to be a similar where their sensory level also is, so it may have some association with just the sensory difference there. To my knowledge, no one has ever confirmed actual tightness like an actual constriction of the muscles there, it's just a sensation. But it's still something that's not perfectly understood.

[00:45:37] **Audience Member 7:** So do you treat it as neuropathic pain or spasm?

[00:45:47] **Dr. Kyle Blackburn:** That's a really fascinating question. So I can honestly say we have sometimes treated this with agents that we would use for neuropathic pain and sometimes for spasticity. The reality is there are no randomized trials telling us how to do this, it's really experience-based. So we've used agents for both, depending on what's appropriate and responses are also variable. It's an area where we really should do some digging into how we can help because it often is a bothersome symptom for people.

[00:46:17] **Audience Member 8:** Do we have time for two more, Doctor?

[00:46:19] **Dr. Kyle Blackburn:** What do you think?

[00:46:23] **Audience Member 9:** I'm wondering about the terminology for idiopathic. Is there like a statute of limitations on when - mine's 20 years post and it's always been idiopathic transverse myelitis? And in the back of my mind, I want to know the why. So is there a time frame on - is it too late for me to do the advanced or -

[00:46:45] **Dr. Kyle Blackburn:** That's a really good question. And theoretically, no. In most cases aquaporin-4 would have declared itself at this point, I don't want to say anything is absolute. There are a number - as we talked about the MOG antibody can be a one-time event. And sometimes that antibody drifts out of the system and is gone. So it may be hard to diagnose. The further out we get from an event, the harder it is to revise a diagnosis if there's only been a single event. So unless you have the early imaging and someone says this

is actually a spinal cord stroke, it's very hard to revise a diagnosis of an inflammatory disorder this far out.

[00:47:27] **Audience Member 10:** Have you found any relationship between COVID on this type of diseases, spinal cord diseases?

[00:47:37] **Dr. Kyle Blackburn:** I think that would be another hour of talk honestly. It's very complicated but we do see people who develop a optic neuritis or are diagnosed with MS or all of these diseases at the time of COVID infection. Now, there was a time when COVID was widespread and some of that could be argued, coincidental, they were going to develop this, but that was the time. But we do believe that we - and we've known for years that certain infections may increase the risk of something like this happening. I just talked about ADEM where somebody had a diarrheal illness and then had ADEM. So it is definitely possible that the COVID was that last straw that led to this happening. We believe that it may have been in somebody who's already susceptible, but that certainly seems to be the case that COVID could be a last straw for these things to happen.

[00:48:29] **Audience Member 11:** Actually, we came to this conference because our son has MOG but we also have a daughter. His sister is 2.5 years younger who they're trying to determine between ankylosing spondylitis and maybe multiple sclerosis is there. Can you talk about that?

[00:48:44] **Dr. Kyle Blackburn:** Sure. So in this specific situation, they're talking about a disease that involves the joints in the lower parts of the spine versus a disease that involves the nervous system that's usually resolved with MRI scans if they're able to be done. With multiple sclerosis, we see typical findings on MRI scans. So an MRI of the brain or spinal cord could be helpful there. Thank you all so much.