Diagnostic Criteria for Typical and Atypical Presentations

You can view this presentation at: youtu.be/Rz240YFf76s

[00:00:00] **Dr. Benjamin Greenberg:** Hello, my name is Dr. Benjamin Greenberg. I'm a professor of neurology at the University of Texas Southwestern, where I lead our transverse myelitis program and rare neuroimmunologic disorders programs. And I'm happy to be talking with everybody today about an introduction to these disorders that I refer to as the alphabet soup of rare neuro immunologic disorders.

[00:00:27] Whether you've been told you've had optic neuritis (ON), neuromyelitis optica spectrum disorder (NMOSD), acute flaccid myelitis (AFM), transverse myelitis (TM), AQP4or aquaporin-4 mediated disease, MOG or MOG associated disorder, or my favorite acute disseminated encephalomyelitis or ADEM. We're often left perplexed as to why one individual fits into one category while other individuals fit into others.

[00:00:58] And how exactly do clinicians differentiate between these disorders? Unfortunately, the nomenclature is not only confusing to patients, families, and loved ones, but often it's confusing to clinicians as well. It's not unusual for me to see patients in clinic who were told that they have one disease only to leave my clinic with a different label.

[00:01:21] So I thought it would be useful to present to everybody in our community the approaches we take when trying to categorize individuals into this alphabet soup. By no means is this talk meant to be exhaustive. As we talk about each of these disorders, we can talk about diagnostic criteria, but I want to give a 30,000-foot view as to what differentiates individuals within these disorders and where there are gray areas.

[00:01:47] So it's helpful to understand the different ways we could classify an individual's neurologic journey into one of these nice tidy boxes of a name. And in general, there are three different ways that we can classify an individual into a category. The first is based on anatomy. So, your nervous system has two broad parts to it, the central nervous system and the peripheral nervous system.

[00:02:15] Everything we're gonna talk about today has to do with the central nervous system. The central nervous system is made up of both the brain and the spinal cord but also includes some of the nerves that exit the brain, cranial nerves. And the one that we focus on the most is the optic nerve. So, for the purposes of our community, the important three gross anatomic structures to know are the optic nerve, which is the connection between the eyeball and the brain.

[00:02:46] The brain itself, which includes the top part of the brain and the bottom part known as the brain stem, and then the spinal cord. That includes the cervical, thoracic, and lumbar sacral spine going from top to bottom. Now those are the gross anatomic structures that form the basis of the central nervous system.

[00:03:06] If we look within the brain or within the spinal cord, there is also a differentiation of clusters of cells. And when the cell bodies, what are known as the nuclei of the cells cluster together, we call that gray matter. And where we see long connections between cells, we refer to that as white matter.

[00:03:26] What you see here in section, is a piece of spinal cord that has been stained in such a way that the gray matter appears dark. That butterfly shape in the middle is the gray matter of the spinal cord, and the white matter surrounds it. So, within the anatomic classification of disorders, neurologists will ask the first question, has an individual had inflammation of the optic nerve brain, spinal cord, or a combination of those three?

[00:03:58] And when looking within the spinal cord, and when with looking within the brain, we ask, was it the gray matter or the white matter? So, as we get to different disorders, I'm gonna keep track for you whether or not the disorder affects the optic nerve brain or spinal cord, and whether or not it affects the gray matter or the white matter.

[00:04:17] But this anatomic approach to classifying individuals is only one of three different ways we think about conditions. The next way we categorize individuals is based on time and specifically whether or not somebody has had a single event in their history, or if they have had recurrent inflammation over time more than once.

[00:04:39] And in general, this is not a hard and fast rule, but in general, the two events need to be separated by at least 90 days. So, if an individual comes in on the first of the month with optic nerve inflammation, but by the middle of the month has developed spinal cord inflammation, we categorize that as one global event and the clock starts for 90 days.

[00:05:01] If they come back six months later with a new event, we now classify them as having recurrent disease. So monophasic or one-time inflammation includes all of the events that happen within 90 days of each other, whereas events that are separated by more than 90 days are classified as recurrent disorders.

[00:05:23] The third possible way to classify individuals, which is definitely our preferred way, when possible, is based on biology. If somebody comes to me and they say, I want to know if I have high cholesterol, I check a lipid panel, I check their cholesterol levels, I don't measure their blood vessels. I don't ask them how fast they can run a mile; I don't look for hints or surrogate measures of those biologic processes.

[00:05:49] I measure the biology directly. So, it would be great to have an easy test to differentiate individuals based on what part of their anatomy is gonna be affected, whether it's gonna happen once or more than once based on a blood test or based on a biology. But those tests are very limited in the category of rare neuroimmunologic disorders, and so we've only been able to apply them to a couple patient populations.

[00:06:13] However, as I'll point out, where we are able to do testing based on biology, our understanding of the disorders, our understanding of the patient experience, our understanding of the needs and approach to management are greatly expanded. And indeed, this is where a lot of our research focuses, is understanding the bio biology, because when we do that, we can better treat individuals and support them through this journey.

[00:06:38] So let's take each of these three classifications schemes and look at how they live independently of each other and how they intersect. So based on the multiple ways to classify disorders, I wanna start with anatomy. So, let's talk about the different parts. The spinal cord, white matter, the spinal cord, gray matter, the white matter of the brain, the gray matter of the brain.

[00:07:01] And then within the optic nerve, I've artificially separated it between the myelin sheath, which forms the white matter and the axons, which it surrounds. That's a little bit of an artificial separation. Any inflammation that affects the optic nerve in general affects both the myelin and the axons, but possibly to different degrees depending on which disorder we're talking about.

[00:07:23] If, however, we think about time course, we're gonna separate the disorders based on those that are in general monophasic happening one time and one time only, versus those that have a known high risk of recurrence over time. And then finally we're gonna talk about biology. And there are lots of different biologies that can lead to inflammation within the central nervous system.

[00:07:47] And I wanna define some of the terms we're gonna use and then we'll explore them in more detail. So, first, when we think about the inflammation, the word inflammation, we conjure up images of the immune system fighting infections. And while this is absolutely true, the true definition of inflammation refers to the immune system leaving the bloodstream and entering a tissue.

[00:08:11] So for anyone who's ever cut their hand when working in a garden or in a kitchen or in a workshop, the next day, there's some redness and swelling around that tissue injury. And that redness and swelling are immune cells leaving the bloodstream to go fight the bacteria that live on our skin and to prevent those bacteria from crossing into the bloodstream and making us sick.

[00:08:33] Inflammation can be a lifesaving event when occurring in the proper context. If inflammation occurs out of proportion to what's needed or is activated inappropriately, inflammation can cause damage to the very tissue it's trying to save. What are the different components of the inflammatory system or the mechanisms with which we can activate the immune system relative to these rare neuroimmunologic disorders?

[00:09:02] So the first process we talk about is referred to as post-infectious. In this scenario, the model suggests that an individual who's infected with a virus or bacteria activates the immune system to fight that virus or bacteria. But then after that pathogen has been decimated, that activated immune system goes on the prowl looking throughout all the different compartments of the body and can enter tissue inappropriately.

[00:09:29] So the infection is gone, but the immune system enters by mistake, thinking an infection is there and causes damage. This type of inflammation, we think plays a distinct role in rare neuro immunologic disorders. But we've learned over the years that rarely an immune system can enter the brain or spinal cord in the setting of an infection.

[00:09:54] And in the course of clearing that tissue of the infection can lead to friendly fire damage to the surrounding tissue. And we'll talk about an example of this disorder in a moment. Are there pure infectious causes of these disorders? Turns out that is extremely rare. An infection in and of itself without an immune system response usually does not lead to the disorders we treat.

[00:10:19] However, the components of the immune system that can get activated include cells like T cells and B cells, the soldiers of the army of the immune system, or certain inflammatory proteins known as

antibodies. We're gonna explore each of these in turn and apply them to the different disorders that we focus on in our community.

[00:10:40] Let's get back to the alphabet soup and let's talk about these different diagnostic categories, myelitis versus transverse myelitis, acute flaccid myelitis, optic neuritis, AEDM, MOGAD, and neuromyelitis optica. What is the anatomic basis of separating these things? So, in the beginning, the separations are relatively simple.

[00:11:05] First we start with the spinal cord. If you have spinal cord inflammation, the term that gets used is myelitis. What that means is the immune system has entered the spinal cord either by mistake in a post-infectious or autoimmune pathology, or in a para-infectious pathology fighting off a virus, but in the meantime, causing independent damage to the tissue.

[00:11:31] In general, we refer to acute flaccid myelitis as inflammation of the cord. Whether it's there because of a virus or inappropriately that predominantly focuses on the gray matter of the cord, it can absolutely affect the white matter as well. And in fact, in at least half of our acute flaccid myelitis patients, we see evidence of white matter involvement.

[00:11:53] The predominant focus of the inflammation is the gray matter. The reason this is important is it's a distinct subset of myelitis. Then the group that was classically referred to in the literature as transverse myelitis. And in this group, transverse referred to the sensory deficit that individuals would have where they would say from a level down, they couldn't feel things.

[00:12:17] And indeed, when we looked at the spinal cord across the cord in a transverse plane, there was inflammation. That term transverse got attached to the word myelitis forever, plaguing our alphabet soup. There is an initiative underway and we hope to be published next year to suggest removal of the word transverse because it's often very confusing to individuals.

[00:12:39] We support the approach of defining myelitis as gray matter centric, white matter centric or involving both. But anatomically spinal cord inflammation is referred to as myelitis. Now individuals with myelitis can suffer it because of a lot of different biologies. Some of those are monophasic, some of those are recurring.

[00:13:01] So any individual who has myelitis needs to be tested for possible underlying biology that can lead to recurrence in the future. And we'll talk about what those tests are. If anatomically inflammation occurs within the optic nerve, we refer to this as optic neuritis. It can involve one optic nerve or both, in which case we refer to it as bilateral optic neuritis.

[00:13:29] It can happen because of post-infectious or para-infectious reasons, as well as underlying autoimmune disorders. Whether a person presents with myelitis or optic neuritis, they need tests to determine whether or not they're at risk for recurrence in the future. One of the most confusing diagnostic terms, or I should say one of the ones that gets misapplied more often than not is acute disseminated encephalomyelitis or ADEM.

[00:14:00] By definition, individuals with ADEM have diffuse inflammation of the brain. In addition, they may or may not have inflammation of the optic nerves or spinal cord. Often, we'll see patients, usually children, referred to our clinic with diffuse inflammation of the spinal cord being told they had ADEM.

[00:14:23] In order to make a diagnosis of ADEM, there has to be brain involvement and there usually has to be evidence of symptomatic brain involvement, sleepiness, confusions, seizures, something to show that the brain was affected by the immune system. And it's this brain inflammation that forms the anchor of the acute disseminated encephalomyelitis diagnosis.

[00:14:48] So an individual with just diffuse inflammation of the brain can be diagnosed with ADEM. A person who has diffuse inflammation of the brain and the optic nerves can be diagnosed with ADEM. A person with diffuse inflammation of the brain and spinal cord can be diagnosed with ADEM and a person with diffuse inflammation of all three can be diagnosed with ADEM.

[00:15:09] But an individual who only has inflammation in the optic nerve or spinal cord cannot be diagnosed with ADEM. The brain must be involved. This pattern based on anatomy is critical for neurologists to try and determine the underlying cause of inflammation. There are certain conditions that are commonly associated with ADEM, while others rarely cause that level of inflammation.

[00:15:38] Accurate categorization of the individual based on the anatomy of their inflammation can be critical for an accurate diagnosis. There are other features that we use to determine what category a person should be placed within. Let's focus on biologic definitions of a disease. This requires a testable proven pathology that has been associated with the symptoms and patterns of inflammation that different patients have.

[00:16:11] And in our community, there are really only two disorders that fit these criteria. The first is the anti MOG associated disorder, and the second is the seropositive neuromyelitis optica disorder associated with the aquaporin-4 antibody. So, individuals who have optic neuritis, myelitis, or even ADEM, are often screened, if not always screened for these two antibodies.

[00:16:40] And if a person has a definitive positive test for one of these antibodies, then it can dramatically impact our ability to accurately categorize their disease and predict the future. For example, individuals who have an accurate test for the aquaporin-4 antibody are, by definition told they have neuromyelitis optica.

[00:17:03] Individuals with anti MOG antibodies need to have a little more digging done to determine the most accurate diagnosis. And the reason for this has to do with what an antibody is and how we test for it. So let me divert for a moment and just give you a little bit of background about what an antibody is.

[00:17:23] So an antibody is a protein that is produced by your immune system to fight infections. And on the right hand of the screen, I have an image of a cruise missile being launched from a submarine. What do these two things have in common? So, an antibody is the most sophisticated smart cruise missile ever created.

[00:17:46] What do I mean by that? Let's imagine that you really hated somebody named Joe, and you were very angry at Joe, and Joe was off traveling throughout the world, and you really wanted to drop a bomb on Joe's head, and you're somewhere else in the world and you want to try and reach him across the globe.

[00:18:07] If you could launch a cruise missile that would circle the globe all day long, over and over again and never ever, hit anybody but Joe, this would be an incredible weapon. You could launch it on a Wednesday and forget about it for months. And only when the cruise missile saw Joe and only Joe in the crowd would it drop on Joe and only injure him leaving everybody else safe.

[00:18:36] This would be a remarkable cruise missile. For anybody in the defense industry, you can make a lot of money if you were to create this. Mother nature beat us to the punch with an antibody. An antibody is a protein that your B cells release into your bloodstream. They can float throughout your blood for days, weeks, months.

[00:18:57] And only when they find the protein that they were designed to attack will they attach that protein and blow it up. So, if you have an antibody against strep throat, Influenza, COVID, measles, or any of the pathogens that we interact with on planet Earth. Once your immune system has been trained and created

an antibody to recognize and fight that infection, you are forever protected or almost forever protected from that pathogen.

[00:19:27] The antibody can persist in your blood or get recreated by B cells over time and will never do any damage to you unless it targets that protein, whether it's flu or COVID or strep throat. What happens if an antibody is produced by mistake that targets a natural protein within your cells? What if the immune system by mistake creates an antibody to a protein called, MOG, which lives on the myelin coating the axons of your optic nerve brain and spinal cord?

[00:20:05] What if your body by mistake makes an antibody to the aquaporin-4 protein that lives on various cells throughout the optic nerve brain and spinal cord? If that antibody is produced and gains access to the central nervous system, it can attach to that protein thinking it's a pathogen and lead to destruction of the very tissue your immune system is supposed to protect.

[00:20:30] This is the definition of an autoimmune disorder. A, an immune system that has gotten confused and an error started producing a response, in this case, an antibody to the tissue that it's supposed to protect. So, for individuals where we can prove that this antibody exists, we can classify them as having an anti MOG associated disorder or an anti-aquaporin-4 associated neuromyelitis optica.

[00:20:57] But the trick is in the testing. So, if I were to line up all of the cruise missiles from a submarine just by looking at them, I can't tell their programming. I can't tell what they're supposed to attach to. And indeed, when we take out a person's blood, if we look under a microscope, there's no way to tell what antibodies there from a specificity perspective..

[00:21:22] So how do we test an individual for antibodies to the MOG antigen, the MOG protein, or the aquaporin-4 protein? There are lots of different technologies that we can use to test for an antibody, but none of them are foolproof. So, when we're looking at technology to screen your blood. For autoreactive antibodies, what we do is we take the protein of interest, the protein that we are curious about if you've developed an antibody against it.

[00:21:55] In this case, let's talk about the MOG protein. And we can take that protein and stick it on a plate, or we can have a cell, a live cell, express the protein, and then we mix your blood with that plate or with those cells. And then we add in a secondary protein to highlight anytime your antibodies stick to the MOG protein.

[00:22:21] You can think of it as a criminal lineup. Does, do any of your antibodies fit the description of the criminal antibody? Do they stick to the plate? Indeed, if you have a lot of antibodies that strongly stick to the protein, we're gonna be able to detect it in your blood. But how could this testing give you an inaccurate result?

[00:22:46] Where are the inadequacies within testing and what are the ways that we can be fooled? We refer to these as false positives and false negatives, and it depends on the test. There are different technologies to screen for antibodies, and these technologies have different batting averages. Some are better than others.

[00:23:08] So when we think about false positives, it has to do with the cutoff that we use to determine if an antibody is sticking. What do I mean by that? So, let's go back to the criminal lineup. So, let's say you have a test with a very good eyewitness and they say, yep. Number three is the criminal. No question about it.

[00:23:31] I saw that person from every angle. That is your criminal. You can be very sure that person was the one who committed the crime, and you have a high degree of confidence in the test result. But what if you see someone for a brief moment from the side and it, there, the antibody only weekly binding to the plate.

[00:23:53] Maybe it binds the protein, but maybe it just got stuck there by mistake. Maybe our confidence in the result isn't as high. So, when we're judging antibody tests, we set cutoffs and we say we have to be a certain percent sure to know that the antibody is really there and sticking to the protein and isn't just getting stuck in the background by accident.

[00:24:17] These cutoffs aren't perfect. So, it's possible for somebody to have a false positive because maybe they have an antibody that sticks by mistake just enough. Likewise, you can have a false negative. What if the day before the test you got a medication or a procedure that lowered your antibody levels? And on that day, there weren't enough there to stick to the plate.

[00:24:42] So we have to take into the context when and how a test was done before we definitively diagnose somebody with an anti MOG associated disorder or an anti-aquaporin-4 disorder. And the reason it's critically important to get that test right and to interpret the results correctly is individuals with those antibodies have a different risk of recurrence in the future.

[00:25:09] And this gets me to the last description of disorders, and that is descriptions by time. Those that are monophasic and those that are recurring. And what's confusing is regardless of your label at the beginning, you might fit in any one of these categories. What do I mean by this? So, individuals who test positive on a reliable test with a reliable cutoff for the aquaporin-4 antibody are presumed to be destined for a recurring disease.

[00:25:42] In fact, if you have one event of optic neuritis or myelitis or brain inflammation and you test positive for the aquaporin-4 antibody, the general recommendation is you should go on a medicine to prevent recurrences because statistically your risk is so high, it's not a hundred percent. There are individuals who can have one-time events in the setting of an aquaporin-4 mediated disease, but they're so rare we recommend everybody go on immunotherapy.

[00:26:12] But let's compare that to anti MOG associated disorder. So again, an individual who had optic neuritis, myelitis, or ADEM and tests positive for the anti MOG antibody, it turns out that some of those individuals will right the wrong of the immune system. Over time, that antibody may disappear and their risk of recurrence goes down significantly.

[00:26:35] Indeed, for those individuals who have an antibody that persists for more than a year, there are many of those individuals, not all, who will go on to have single events in their life. So not everybody with the anti MOG antibody requires treatment. We don't know who's who. So, the general rule of thumb currently in clinic is to treat individuals with preventative therapy who have had more than one event if they're positive for the anti MOG antibody versus those with the anti-aquaporin-4 antibody who get treated after their very first event with preventative therapies.

[00:27:12] Now, for all those individuals who wound up in the recurring category, they had a first event. That event might be myelitis, it might be optic neuritis, it might be ADEM, or it might be some other manifestation of the anti MOG antibody. And there are others. And for those individuals who've had one event, we have to test them to determine what are the odds they're gonna have recurrence, checking the anti MOG antibody, the aquaporin-4 antibody, and other tests.

[00:27:40] Helps us to determine what are the odds that individuals with these disorders will wind up in the monophasic or recurring category. And indeed, when we look at the monophasic category, idiopathic myelitis, idiopathic optic neuritis, idiopathic ADEM are individuals who have had one of those disorders and tested negative for both the MOG and the aquaporin-4 antibody.

[00:28:04] And indeed, those individuals have a low risk of recurrence in the future and are most likely monophasic. We're only positive in retrospect, so we have to follow patients for a period of time to ensure they don't have recurrence. But overwhelmingly, the risk is low. You'll notice on these descriptions by time, there's one diagnostic category anatomically I haven't listed, and that's acute flaccid myelitis.

[00:28:30] The myelitis in the spinal cord that affects the gray matter only, Rarely this condition can be caused by the anti MOG antibody. And if you're positive for the anti MOG antibody, those rules apply. You have to be watched for recurrence over time. But if your acute flaccid myelitis was para-infectious, something we saw with the enterovirus between 2009 and 2018, those individuals are almost by definition monophasic.

[00:28:59] I'm not aware of acute flaccid myelitis patients outside the setting of the MOG antibody having recurrent disease over time. Families can rest assured that we are not seeing recurrence in our AFM patients who had viral mediated AFM. This is quite an alphabet soup. Hopefully I gave you a way to navigate through it and decide what category applies to you or talk to your physician about whether or not your categorization is correct.

[00:29:27] Why do we spend the time and have a community that has such a big tent approach to involving individuals with such a diversity of diagnoses? Speaking as a scientist, it is important that we stick together. There are biologic questions that can only be answered together. In fact, recognition of the anti MOG antibody as a pathogenic antibody only occurred because we recognized neuromyelitis optica patients who tested negative for the aquaporin-4 antibody had certain phenotypic features. This allows us to draw novel insights when we compare different individuals who are in different diagnostic categories. It allows epidemiologic studies around rare disorders to achieve a certain size so we can understand the prevalence in a better way.

[00:30:15] And outcome measures that we use for clinical trials are enhanced if we can compare and contrast different groups. And so, by having a big tent approach within our community, we advance science in meaningful ways. Clinically we need to stick together because we learn a lot from each other. Relative to symptom management, knowing what works for a myelitis patient, whether it was because of the anti MOG antibody, the aquaporin-4 antibody, or just idiopathic.

[00:30:44] What I learned from one applies to many. Similarly, when we get to rehabilitation and preventative strategies, the comparing and contrasting of individuals in my clinic in a systematic way makes me a better clinician and enhances the ability of my team and health professionals around the world to give the most accurate advice on how to approach management of these disorders.

[00:31:07] Then finally, politically, we need to stick together. Now, don't get nervous. This is not a political statement of normal US politics. This is the politics of healthcare, and we belong to rare disease communities and rare diseases get the least amount of funding and support. When we coalesce together and we find commonalities in rare diseases, resources can be augmented and shared, and everybody can benefit relative to the work that gets done scientifically.

[00:31:35] When I started in this field, my daughters were, on the left, very young. They've grown up into beautiful, smart, amazing young women, and they still push me every day in terms of asking why we haven't made more progress. I'm now able to tell them we've actually made a lot of progress. If at a minimum, getting people into the right category.

[00:31:54] And by doing that, advancing our ability to prevent recurrences, improve symptomatic therapy, and really funnel our attention into the work that needs to be done to cure these disorders.