Rare Neuroimmune Disorders

Diagnostic Criteria

You can view this presentation at: youtu.be/aS-Wr3eZSiw

[00:00:04] **Shruti Mahale:** Hello, everyone. Thank you for being here. Really enjoyed listening to the clinicians talk a little bit about the difficulties with the diagnosis process earlier this morning, and it was really humbling to hear some of you share your experiences with the diagnosis process. My name is Shruti. I'm a 4th year medical student at UT Southwestern.

[00:00:28] Today, I'm going to be talking to you a little bit about a project that we've been doing related to patients with rare neuroimmune disorders. The patients who were involved in the study had rare neuroimmune disorders, specifically including, acute flaccid myelitis, transverse myelitis, optic neuritis, acute disseminated encephalomyelitis, MOG antibody disease, and Neuromyelitis Optica Spectrum Disorder. The field of neuroimmunology, as mentioned earlier this morning, has made a lot of advancements and progress in the last few decades.

[00:01:10] This has especially been the case with the discovery of various antibodies against neuronal and glial antigens. The discovery of these antibodies has helped with the overall diagnosis process of rare neuroimmune disorders. Specifically, typically when we suspect that a patient has NMOSD or MOGAD, we try to test for aquaporin-4 antibodies as well as MOG antibodies and this has helped with the overall diagnosis process.

[00:01:41] However, despite these advancements, diagnosing rare neuroimmune disorders continues to remain challenging. A lot of these patients tend to have symptoms that are seen in other neuroimmune conditions, including multiple sclerosis. This can make the overall process very long for patients in terms of trying to get a definitive diagnosis, and it must be very challenging for providers as well.

[00:02:07] Conditions such as transverse myelitis and optic neuritis are also seen in conditions such as multiple sclerosis, but they're also seen in conditions such as MOGAD and NMOSD. This leads to the overall confusion. A lot of patients are also diagnosed as idiopathic when the cause of these symptoms remains unknown. Many patients are also labeled as seronegative when they don't have those antibodies.

[00:02:37] So, all of this to say that diagnosing rare neuroimmune conditions remains challenging, but it's extremely important for patients to have a definitive diagnosis, for effective treatment and management, and it's also very important for them to understand their condition. So, there tends to be a lot of confusion,

at the time of diagnosis. Many patients as discussed earlier this morning have been diagnosed in the past with conditions such as MS, Guillain Barre syndrome, and there's often a revision of diagnosis, and this can affect their overall understanding of their disease.

[00:03:14] Health literacy and education has also been known to play a role in a patient's understanding of their condition. Through our study, we wanted to better assess how much patients with rare neuroimmune disorders understand about their condition. For our study, we had some neuroimmunologists at our institution, come up with a questionnaire, that was initially administered to around 5 patients, who gave us some feedback after which we revised our questionnaire and made changes accordingly. It was made up of four sections.

[00:03:47] The first was the demographic section. We collected information such as the patient's age at which they were diagnosed, their gender, their educational level, whether or not they had a history of misdiagnosis. Our second section was the test of knowledge. So, we looked at things such as the localization, whether or not the patient knew the etiology of the condition they had, symptoms associated with their condition, as well as what constitutes a relapse and whether they could identify risks associated with relapses.

[00:04:19] Our third section was the METER. This is a quick way of looking into health literacy. It's a set of terms, some of which are random, some of which are medical terms, and the patient is asked to identify the medical terms. And then finally, we had the Patient-Determined Disease Step Test, which is a question related to the patient's mobility and let us know a little bit more about the severity of their condition.

[00:04:41] So, this questionnaire was administered electronically via a REDCap survey, and patients could either take the survey in the clinic, or at home, or via social media. In terms of our results, we had a total of 102 patients who were enrolled in the study, of which 92 completed it, and we had 85 who completed all four sections. In terms of our demographics, the median age of the people who took the test was about 56 years of age.

[00:05:12] We had a majority of female respondents as well as white respondents. In terms of educational status, the majority of our respondents had 16 plus years of education, which is equivalent to a bachelor's degree, so highly educated. Then in terms of the diseases that were reported, a majority of our respondents reported having transverse myelitis.

[00:05:32] We had around 12 respondents who reported having more than one diagnosis, which we expected. We had two patients who were noted to have ADEM, of which one of them reported having both ADEM and MOGAD. In terms of our test scores, generally speaking, we had an increase in the test of knowledge scores in patients who had NMOSD and MOGAD as compared to those who had idiopathic conditions.

[00:06:00] We also found that patients across all groups did well on the METER, meaning that their health literacy levels were relatively high. In terms of conclusions, we found that individuals with idiopathic conditions, specifically transverse myelitis and ADEM scored lower on the test when compared to those with better characterized conditions such as NMOSD and MOGAD.

[00:06:24] Our population had a proportion of individuals with higher education level, as well as health literacy, and this may not be representative of the whole population. Sorry about that. Then we found that patients with vision loss may require additional accommodations, and they may have had some barriers to completing the survey. Individuals with idiopathic conditions may benefit from targeted educational resources into better understanding their condition as well as understanding more about relapse risk.

[00:06:51] We hope to further analyze some of the results, that we obtained from the study and better understand the relationship between our test of knowledge as well as disability scores and, some of the other things that we looked into. Thank you.

[00:07:17] **Dr. Kyle Blackburn:** Well, thank you all for having us today and thank you all again for letting Shruti share this data. We thought this was a nice segue from what we've been talking about before, and kind of what we're going to talk about next, which is a little more of a focus on diagnostic criteria and why we kind of harp on those very importantly and why we probably need some revisions to some of our criteria at times.

[00:07:40] So, just to kind of set the stage and I think we've heard about these quite a bit up to this point, but, diagnostic criteria the formal definition is the set of signs, symptoms, and tests that are used to facilitate diagnosis of a condition. As an example, I have a set of diagnostic criteria for a common condition called headache. Usually, the way we craft diagnostic criteria are a group of expert clinicians get together and there are a variety of methods now through which you can do this, but you try to arrive at a consensus where most people agree this is the minimum threshold you need to make the diagnosis accurately.

[00:08:22] Often diagnostic criteria, as you've heard about today, they undergo multiple revisions as science advances, as we get new biomarkers, as we get better at identifying subtypes of different diseases based on a clinical syndrome, we actually make revisions to those diagnosis and maybe parse out other diseases as we'll talk about happened, with some of these diseases today.

[00:08:45] We just make our diagnosis a little more firm. These should be updated frequently, because advances in the field and the goal is just to make sure that we're making the right diagnosis and ideally making it early, especially in the case of rare neuroimmune disorders where there's often acute inflammation. I'm going to draw a corollary from one of the diseases that we see a lot in neuroimmunology and that's multiple sclerosis.

[00:09:19] It's just one of the well characterized diseases. It actually has a history dating back years, but I'm not going to show you the entire history of MS criteria. I'm just going to really show you the 21st century. The criteria for multiple sclerosis, the last several iterations have been rephrased the McDonald criteria. There's actually a set that just came out.

[00:09:36] I was on parental leave in the month they came out, so I haven't gotten a chance to dive into them deeply. You can see if you read these over time, this is specifically talking about a criteria for dissemination in space. How we would define, if somebody has multiple lesions that we expect in that condition. Over time if you watch these criteria you're going to see it gets the number of spots that someone has to have to qualify for that diagnosis decreases.

[00:10:07] As we got better at interpreting MRI and understanding multiple sclerosis and how important it was to treat people with multiple sclerosis early in their course, the criteria evolved. We make it easier and easier to make that diagnosis. The barriers to making an MS diagnosis are much fewer than they were back in 2001.

[00:10:32] The lesson here is continued revisions to the MS criteria have allowed for earlier fulfillment of space and time, which has allowed for earlier diagnosis. In this case, people were treated earlier in their course. I'm going to show you the story of neuromyelitis optica, which I think a lot of people talked about before this.

[00:10:52] So, we're going to get a little historical here because this is one of the diseases we're interested in here. The first descriptions of neuromyelitis optica probably predate, we what you may may have heard of

as Devic's disease. That's when it got the eponym, but there were descriptions of this case of NMO probably preceding this for many years. In Lyon in 1894, they kind of compiled a series of cases that had been reported historically, and they took a patient and actually did a pathology study.

[00:11:21] Kind of a clinical pathology study and that was Doctor Gault's actual thesis. That was kind of the first important step in the definition of neuromyelitis optica, but there were many debates about NMO over the years. I think many people debated because pathologically they argued in many cases, it doesn't look distinct from multiple sclerosis using the pathology that they had at the time. They felt that this was just a variant of multiple sclerosis.

[00:11:52] So, it was still somewhat of even in the 20th century we're wrestling is NMO a distinct entity or is it just kind of a clinical subtype of multiple sclerosis. Of course, there was a debate about whether relapses are important and whether relapses qualify for NMO or whether it should be truly what we call a monophasic course. So, should this all happen to you at one time, or can this happen over a series of years?

[00:12:16] Then really at that point, it was kind of thought this is a disease that affects the optic nerve and the spinal cord. It does not affect the brain or the brain stem or actually there's some debate about how much that was called because the original cases do talk about that some. A lot of criteria said you can't really see brain or brain stem involvement. And then there was a debate about should you have bilateral or unilateral.

[00:12:37] So, in both eyes or a single eye optic neuritis to qualify for this diagnosis. So, NMO kind of lived under this umbrella, really wasn't well appreciated, it wasn't clinically characterized as well. I'm going to fast forward to the one of the important steps in NMO classification. That was really in 1999 when investigators at the Mayo Clinic started to look at NMO patients that they had classified and said, what do these patients share in common? What are we hearing from them? This led to the establishment of clinical criteria for NMO.

[00:13:16] So, this predates aquaporin-4 antibody discovery or MOG antibody discovery, but it was an attempt to say NMO is a distinct disease, and it should stand on its own right, but it was done clinically. I always like to point out, just to kind of show you how much progress we've made. In 1999 the patients that had been historically seen at the Mayo Clinic, of those that had relapsing disease, there was a 33% 5-year mortality rate.

[00:13:42] So, about one in three patients would pass away from NMO at that point. So, it was quite a serious condition. At that point though, the criteria still required you to have optic neuritis in addition to a myelitis and other supportive criteria, and did emphasize the absence of brain lesions. So, this was the current criteria that we had to diagnose NMO. Then the major thing was the aquaporin-4 antibody.

[00:14:11] So, once that was discovered and it clearly defined aquaporin-4 autoimmunity as a separate disease for multiple sclerosis because we don't see aquaporin-4 antibodies in MS. So, it really helped us separate that out and say, NMO is indeed its own disease. It is not multiple sclerosis, but it also allowed us to learn what are the presentations of NMO. In a way of aquaporin-4 autoimmunity. In this case, now that has become synonymous really with NMO for many people.

[00:14:43] We learned that aquaporin-4 positive patients can have unilateral optic neuritis. They can certainly have relapses. This is not necessarily a monophasic disease. In fact, it is frequently a relapsing condition. So, unilateral optic neuritis, one eye optic neuritis can happen. You can have separate distinct transverse myelitis. You can have a wide variety of brain and brainstem lesions. So, it turns out the phenotype was much broader and there were patients that come to us, and I show you pictures of some MRIs from some of my patients, who have been diagnosed with neuromyelitis optica who first presented with a brain or a brainstem attack.

[00:15:18] So, it just really was not, some of them were only recognized to have NMO when they had the typical features of an optic neuritis or a TM, but some of them were able to capture them early and prevent further disability from happening. So, it's really a win. Now our current NMOSD criteria, I know these things are hard to read, but I have a picture of them there on the right, and they capture this. So, they talk about the core clinical features of NMOSD, which do include this myelitis and this optic neuritis that we understand even more now, but it also talks about brain stem lesions and the area postrema syndrome.

[00:15:53] The idea that people can have intractable nausea and vomiting with this condition. It talks about the fact that you could have brain lesions in characteristic areas for NMO. And it still allows for that diagnosis to be made for those patients that are antibody negative. It allows for, of course, in instances where aquaporin-4 testing is not available we still need to have that. It's an important part of these criteria. So, in summary, what we have learned from NMO is taking this diagnosis, and we have kind of broadened the phenotype.

[00:16:26] We have been able to identify these patients really now at a single clinical attack that has improved our ability to treat this condition. Discovering this antibody also made a lot of other progress, but by revising our criteria we're diagnosing this condition earlier. We're diagnosing it better. We're recognizing a broader range of patients. We're able to treat them, and that's the wonderful thing about these criteria. It's really one of the success stories of this field.

[00:16:51] So, now we're going to go to the MOG antibody, which story has kind of been evolving over several years and decades honestly. So, when you look at early studies of MOG antibodies there's kind of this interest in MOG. For years it had been known, based upon experimental models of multiple sclerosis that are called EAE, that if you make a mouse to have an immune response to the MOG antibody, it causes problems. So, they thought, this is very relevant. This must be what the holy grail for multiple sclerosis. It didn't quite pan out that way.

[00:17:24] So, early studies of MOG antibodies didn't really find it. Found it in some multiple sclerosis patients, but they found it in also a number of healthy controls and other diseases. There were certainly probably some MOGAD patients in that group, but it wasn't neatly defining them. That goes back to what Dr. Smith was talking about, sensitivity and specificity of a test. It wasn't there yet but through the advent and discovery of a good cell-based assay for this condition, we have been able to refine those studies and found, hey, it turns out this doesn't really define multiple sclerosis, but it does define, I think the first discovery was it actually defines a group of kids with ADEM.

[00:18:01] Then we discovered, well, there's actually optic neuritis and myelitis and all these other things. So, we found that, now we have a good marker. We have evolved to the point that now we need diagnostic criteria for this distinct condition because we recognize MOGAD patients look, you know, instead of calling them a subset of MS or NMO, this disease stands on its own. It has very unique features. It requires a different treatment approach. It requires just a different way of thinking about it. So, it needs its own criteria.

[00:18:36] Fortunately, in 2023, we see that the MOGAD criteria define a new disease. And this has been talked about for years before, but we finally got into defining it. Again, print is hard to read. These things always are wordy but it's important with MOG antibodies specifically. We need to know that the antibody is there, but we also need to know the level.

[00:19:00] Lower levels of MOG antibodies can be seen in multiple sclerosis and other non-diseases. So, in this specific instance, it was very important that the authors also spell out what does MOGAD look like on an MRI clinically. So, they list the symptoms and the MRI features that are typical of patients with high titers of

MOGAD. So that those of us, because the test isn't as specific as an aquaporin-4 test, we want to make sure that we define that. They also said here are some red flags for when you may not be dealing with MOGAD, and your test may be just a weak positive.

[00:19:37] So now we have these diseases that have clearly separated from multiple sclerosis and now stand on their own. I'm going to quickly turn to ADEM criteria to make sure that we touch on everything. The ADEM criteria are clinical criteria based on the presence of confusion. They're based upon MRI's that typically have multiple lesions, and then usually this is a condition that stabilizes after a few months. Now between the last ADEM criteria that I'm aware of are from 2013, and they're certainly important.

[00:20:14] We still can use these criteria to diagnose ADEM, but we do need to separate out, I think they could benefit from a distinction from MOGAD, which has been really well characterized since 2013, and probably an assessment of some mimics of ADEM. I think whenever we're dealing with idiopathic diseases, adding in those red flags is really critical. Now I'm going to turn my attention to the idiopathic TM criteria. They really are the last criteria to get an update.

[00:20:48] So, this is the last time a set of criteria for transverse myelitis and specifically for idiopathic TM were released. It was 2002. I wanted to show you our technology at that time. So, we didn't even have a smartphone. We were using an iPod. So, you can think of it, we're still trying to use an iPod to listen to music in 2024. I don't know that anyone is. If anyone still owns an iPod, I certainly applaud you because it's probably a relic, and you may actually have something valuable now.

[00:21:15] We're going to go through some of the things about these criteria that probably need revision. I'm happy to say that that is an ongoing process, and I'm hoping soon we're going to have a formal set of criteria that show in the 21st century how we actually diagnose myelitis. So, to first show you why these need revision, we have to turn our attention to acute flaccid myelitis, which is, obviously been a phenotype that as we talked about has existed for some time but really came to our attention in the last decade.

[00:21:46] AFM is of course, largely, an infectious disease, associated with enterovirus that can be seen with other variants. One of the striking things about this condition is that it, unlike what they've defined as the idiopathic criteria for transverse myelitis, this is a disease that can actually affect a single limb. So, a person could have it in just one arm affected and very little sensory involvement. Usually, we think of myelopathies as causing sensory levels and those are actually things that are listed very strictly in the idiopathic TM criteria of 2002.

[00:22:13] So, unfortunately, patients with AFM, while we do recognize them as a distinct group, they don't currently fit some of the thinking about inflammatory myelopathies, at least that are published. So, this is one of the reasons we need to update our criteria. Also, as we've talked about before, we are no longer using iPods, and we've got a lot of other tools in the shed since 2002. So, aquaporin-4 and MOG have come available.

[00:22:46] They've defined new demyelinating disorders. Both of those can cause myelitis and are really important that are included in a workup for myelitis in my opinion. We recognize sarcoidosis as an inflammatory myelopathy a lot better than we did in 2002. There's been better classification because of a lot of the work of people here today to define how spinal cord infarcts present and look on MRI, how fistulas, vascular myelopathies look on MRI.

[00:23:11] So, we are better at recognizing those, and it's critical. We don't want to give immune therapy to these patients. We want to offer different forms of treatment. And then of course, as we talked about AFM has this motor predominant presentation. It doesn't always have sensory involvement, and it's frequently

asymmetric and can be actually just in one limb. So, that conflicts with current inflammatory myelopathy criteria. So, to kind of wrap things up, kind of the view for myelitis, in the next couple of years beyond dropping the transverse, which we don't have to talk about anymore. If you've been here, you've heard us talk about that for years now.

[00:23:50] Beyond dropping the transverse, the criteria need to define what an inflammatory myelopathy looks like and what myelitis typically looks like. So, that's probably the first step. We have to define the progression of myelitis, so that clinicians can take these two things and pair them together and say this person I think is having inflammation of the spinal cord and then provide a diagnostic framework to figure out what's going on.

[00:24:12] Define some of these diseases or at least highlight the definitions that exist for aquaporin-4 and MOGAD let's say. And so, highlight those definitions, define other red flags that suggest myelitis mimic as I talked about with ADEM, and as the MOGAD criteria do. Then we also have to provide this working definition for what is idiopathic myelitis. Even though we've made a lot of progress, there still are people for whom their inflammation is really an unknown cause.

[00:24:41] I'm going to stop there because I am a little over. Actually, I just got that on time, perfect. So, you all are here. I think I may have mentioned this even last year when we did the regional RNDS, but, you're here at an interesting time of year. It's the state fair of Texas. So, get out there and explore interesting food that you'll never get a chance to see again. So, all right, thank you all.