Transverse Myelitis (TM)

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Dr. Olwen Murphy: [00:00:04] So thank you for the opportunity to speak today. I'm going to give a little bit of a talk on spinal cord disorders. We're going to focus on transverse myelitis and how things have moved on a little bit from even just the concept of a transverse myelitis. My name is Olwen Murphy, I'm an assistant professor of neurology at Johns Hopkins.

[00:00:27] So this is just what we're going to review briefly today. We're just going to talk about concepts surrounding spinal cord disorders to start with. Then we're going to talk about how things have evolved in the last few years from a blanket diagnosis of transverse myelitis to diagnoses of more specific spinal cord disorders and how that can help people. We're going to review some important research updates then to finish out.

[00:00:55] So transverse myelitis is a term that's been around for a long time. It was applied to many patients, who presented in the past with spinal cord disorders. If we even think just 20 or 25 years ago, we had a very limited understanding of these conditions. There was an idea of idiopathic transverse myelitis, which is really the term used when we don't know what causes something. And many patients who presented with spinal cord problems were labeled as idiopathic transverse myelitis without a real understanding of what that condition was. There was some knowledge about specific causes of spinal cord disorders such as multiple sclerosis, neuromyelitis optica, and some other rare conditions, but things have really evolved a lot in the last 20, 25 years.

[00:01:50] We now have developed many specific markers of diagnoses that we can make in the clinical setting. One of the first advances was made with the identification of aquaporin-4 antibodies in the early 2000s. And that enabled us to make a diagnosis of neuromyelitis optica more specifically in many patients, allowing important treatment. Over time, more antibody markers or blood tests have been identified to be able to diagnose specific inflammatory disorders, like MOG or myelin oligodendrocytes, a protein, as well as rare conditions like GFAP, and other antibodies.

[00:02:24] Sarcoidosis is now an important recognized cause of inflammatory myelopathy and we've become much better at diagnosing this. And then really importantly, it's been recognized that there are actually many

non-inflammatory causes of spinal cord disorders that can be mistaken for transverse myelitis. And it's important to differentiate these in the clinical setting.

[00:02:47] And then you can notice here down at the bottom, our circle of idiopathic diagnoses has really shrinked in size over the last 20 years, that's because we've become much better at identifying a specific cause. We would hope that in the vast majority of patients now who present with an inflammatory myelopathy or even a non-inflammatory myelopathy. Myelopathy is just the term we use for spinal cord disorders in the medical sense. That we can really become better at making a specific diagnosis rather than simply saying this is something idiopathic or unknown.

[00:03:23] AFM, of course, is essential to mention as well, because this has been very important diagnosis that's emerged in the last few years and, of course, many people in the audience or their family members may have been affected by AFM. So how do we come to these more specific diagnoses? Well, the first element is, of course, what's essential in all medical diagnoses. We have to take goods history, ask the person exactly what's happened to them, and the neurological examination. The next element is MRI, it's really essential in making clear diagnosis of the spinal cord disorder and the resolution of MRI has become much better in the last few decades since we can really see with much better accuracy exactly what's going on there.

[00:04:10] And then lab tests as we've mentioned have also been developed, such as the Aquaporin-4 antibodies and the MOG antibodies. So, coupling these things together provides the pieces of a picture that can help us make an accurate diagnosis in an individual. We want to be less like "Sherlock Holmes", and guessing, and deducing things, and we want to be more like the doctors in "Grey's Anatomy" and coming to a clear accurate diagnosis for each patient. And with this approach we can break down spinal cord disorders or myelopathies with much greater accuracy. So, we've got two broad categories. We've got inflammatory, myelopathies, these this would encompass things like aquaporin-4, MOG disorders, infectious myelopathies spinal cord disorders such as acute flaccid myelitis, sarcoidosis, multiple sclerosis, and many other rare conditions.

[00:05:06] And then we have the important category of non-inflammatory disorders, which is increasingly being recognized. So, there's spinal cord strokes, there's vascular malformations in the spinal cord, and then compression of the spinal cord by surrounding structures, and other rare conditions. So now we need to be thinking when a patient walks in the door with spinal cord symptoms, with maybe numbness, weakness, bladder, by all disturbance, we need to be thinking of this breakdown or algorithm in our head. Can we divide it into an inflammatory or non-inflammatory cause? And then can we be more specific in exactly what's causing it? And we've taken this approach at the Johns Hopkins Myelitis & Myelopathy Center now over the last few years and really trying to get to a more accurate diagnosis.

[00:05:57] And we've recently put together this study with the help of the SRNA, based on what's actually happened to the people who have attended our clinic over the last 10 years, how have we been able to be more specific with their diagnosis. And in fact, we found that although all these patients were referred to our clinic with a diagnosis of "transverse myelitis", they were called transverse myelitis. When we actually delve down, we did a good history neurological examination, MRI scans, and laboratory tests, and sometimes further tests, and specific patients. We found that, in fact, in around 1/3 of the patients, they didn't even have an inflammatory disorder at all, and they had a non-inflammatory condition like a spinal cord stroke, a structural disorder such as mechanical compression of the spinal cord. We did find that around 2/3 of patients did have an inflammatory disorder. But in fact, many of these patients actually had multiple sclerosis, which should be more easy to diagnose than some of the rarer things.

[00:07:05] When we delve down into things, we looked at things like neural myelitis optica, sarcoidosis, acute flaccid myelitis. Once we were able to categorize people into all of those conditions, only 12% of the

inflammatory disorders actually were idiopathic or unknown diagnosis in the end. So, I think this is a good improvement and a reflection of where things have come over the last few years that we're reaching a clear accurate diagnosis in the vast majority of patients now and we were able to reflect on this study and how the breakdown of these disorders over the age groups can be an important clinical clue. So, we found that some disorders were more common in children, for example, infection-associated spinal cord disorders like acute flaccid myelitis.

[00:07:58] We also found that other disorders such as vascular malformations of the spinal cord and spinal cord strokes were much more prevalent in slightly older age range, people in their 50s and 60s, for example. Then we're able to look at how the symptoms evolve, which is another useful clinical clue. So, if a person comes to the emergency department and has experienced a very rapid evolution of their symptoms, one moment they're able to walk and then a few hours later their legs are paralyzed, for example, that should make us think of specific problems such as the spinal cord stroke. On the other hand, if somebody comes to the hospital and they've had symptoms evolving over four weeks or six weeks, for example, we need to think of inflammatory disorders like sarcoidosis or idiopathic types of myelitis.

[00:08:54] And why is this important? Well, it's really crucial for us to try and differentiate the disorders, because we are now in the era of modern medicine where we have much better treatments for spinal cord problems. In the past, there may not have been specific treatments for any of these disorders. So, you could argue it didn't matter that much if a person was given the wrong diagnosis, it didn't necessarily affect what treatment they got. But now we're in the era where we have acute treatments for these disorders, and then in some cases, preventative treatments to prevent further attacks of inflammatory disorders. So, taking a diligent approach to trying to diagnose things better, we hope will result in long term better outcomes for the most important people who are the people actually affected by these disorders.

[00:09:44] And so now I'm just going to review some of the recent developments that have occurred in the research that may move this field further forward. There has been interesting articles recently published about immune-based therapies for MOG-associated disorder. So, this is an inflammatory disorder that causes attacks in the spinal cord, or in the optic nerves, or even the brain itself. Patients can have a wide range of symptoms and they may have one attack, or they may have multiple attacks. This is often disorder occurring in children or in young adults, although can occur at any age. So, it's important for a lot of people in our community and it's an interesting disorder in that it doesn't respond to a lot of common immune therapies that we may use for other chronic neurological disorders. And there was a study published that showed that perhaps one of the more promising treatments for these people would be intravenous immunoglobulin therapy, which is an infusion-based treatment, and can help prevent further attacks of the disorder and allow people to live a healthier life.

[00:11:00] On the other side of therapies, we have aquaporin-4 associated disorders. So, this is neuromyelitis optica, again, may affect many members of our community. There's been a huge expansion in the last few years of specific treatments for neuromyelitis optica, and we now have FDA approved therapies to prevent further attacks of the disorder, one of which is Eculizumab, and data has now emerged on the longer term safety and efficacy of this treatment, suggesting that it has a good safety profile and is an effective treatment for aquaporin-4 associated neuromyelitis optica, which is great news for people who may be affected by this disease.

[00:11:44] And then acute flaccid myelitis is another disorder that affects many members of our community and their families, and this is an interesting disorder that's really only emerged over the last 10 years or so. It primarily affects children, and it can cause quite severe paralysis of the limbs and even other parts of the body, like the muscles of breathing. It's called a polio-like illness, because it actually quite resembles historical

cases of polio that of course, is not around much anymore, although there's been an unusual emergence of a few recent cases of polio in America after a long time.

[00:12:25] But acute flaccid myelitis is something that's been very challenging in recent years. And one of the challenges has actually been how to make a diagnosis and how to help our colleagues out there in the community who may be working in pediatric emergency departments and urgent care centers. How can they recognize this disorder? How can they make a rapid diagnosis for children or young people who present with this problem in order to best facilitate their treatment and rehabilitation? So, this was a concerted effort supported largely by the SRNA to bring physicians and colleagues together from institutions around America and actually around the world, and to put our heads together in terms of how we can better diagnose this disorder.

[00:13:14] We came up with a series of diagnostic criteria that we think are going to help over the long term and improving the diagnosis here. And this is important from a research perspective, because if we're going to have studies of potential treatments, for example, for AFM, we need to be able to diagnose the disorder correctly. So, this was a great outcome from the work of the AFM working group.

[00:13:38] And then on the treatment side of AFM, this is exciting news for people in the field and there are early studies, so these are still lab and animal-based studies suggesting that monoclonal antibodies, these are specific type of protein treatments that can be used in the medical setting and they may be effective in potentially controlling the disease of AFM and ameliorating some of the damage that it may cause in the acute setting. So, this is a good step in the right direction that things are being developed in a scientific sense in terms of potential treatments.

[00:14:21] And then there's other rare spinal cord disorders that we now have a better appreciation of, and these are often very treatable. So, one of them is sarcoidosis, this can cause inflammation of the spinal cord, can be quite debilitating and can be a progressive for relapsing disorder across many years. And so, we're thankful now that we have a little bit more information about sarcoidosis-associated spinal cord disorders in recent years, some of which were able to summarize in this study. And we would hope that people with sarcoidosis can avail for more rapid diagnosis now and it's a very treatable disorder with steroids and other types of immune-based therapies.

[00:15:10] And importantly, we need to differentiate the non-inflammatory disorders in order to separate people into better treatment approaches. That's really essential. And then a few years ago there was a suggested diet diagnostic criteria for spontaneous spinal cord infarction or spinal cord stroke, published by our colleagues in the Mayo Clinic, which was a really important development and can certainly help the more rapid diagnosis of these kinds of disorders.

[00:15:42] We also have this other category of patients with non-inflammatory disorders, vascular malformations of the spinal cord, which are an unusual disorder and are really frequently misdiagnosed. This is something we've identified in many of our patients attending at Johns Hopkins. It can take them months or years to come to an accurate diagnosis and they're frequently treated with other approaches like steroids or immune therapies which are not going to help a vascular malformation and may actually do harm. So, this was an important area for us to focus on in the last few years in terms of how we can better recognize people with this problem.

[00:16:27] And then a really important paper was published with the support of the SRNA last year and this was a look at over 4,000 people who had attended VA hospitals with spinal cord disorders and the study highlighted that and this is still quite a common problem. We have a lot of people attend emergency departments and

clinics with spinal cord disorders in some cases the diagnosis is accurate, but this study did highlight that a lot of people are still given this sort of blanket diagnosis of transverse myelitis, and it hasn't always been delved into in terms of the specific underlying problem that can allow better diagnosis and treatment. So, this study was important in highlighting how far we've come, but also that we have further to go.

[00:17:20] And so what does the future look like for spinal cord disorders and most importantly for people with these disorders? We definitely have ongoing improvements in diagnosis which we've highlighted today. It's important that we develop our access to expert care to people across the nation and then in a global sense to areas where there may not be advanced healthcare providers and expertise available. So, the growth of technology and of telemedicine is certainly something that we need to focus more on in this area. Spinal cord disorders are common enough, but not that common that many neurologists will have a lot of experience with them.

[00:18:06] So now that we have specialists with expertise in this area, we need to think more about how we're going to get that expertise out to regions that don't have it. For example, if we have a patient presenting in a state that doesn't have an expert in this field, how can we best make sure that we are available to try and improve the outcomes of everybody across the nation and the global setting? There're important advances that have come and are yet to come in terms of disease specific treatments for disorders such as acute flaccid myelitis and neuromyelitis optica and MOG-associated disorder, and others. So, I think this is an exciting area and rapidly expanding field.

[00:18:53] Of course, people with spinal cord disorders may be left with symptoms and in some cases disability, and it's really essential that we provide long term support and care for affected people and that comes from a medical side of things, and also from the psychological side, from family coping, family support, community support. So, this is really essential work over the long term. Community advocacy is really important for moving this field forward and of course, many of our attendees will have been at the forefront of this. And then the holy grail of modern medicine really is prevention of problems. And one element or one example of this would be, now that we have associated with acute flaccid myelitis, a key link to certain viruses, maybe we could have vaccination of those viruses in future. And this would just be one example of how we could prevent an important spinal cord disorder.

[00:19:58] So medicine is an exciting area and spinal cord disorders are an exciting area. We need to remember that advances don't come overnight. They require the concerted effort of many people across many institutions in the world to make impactful changes for the people on the ground. Atul Gawande is a really important thinker in modern medicine, and I think his words are very apt here. He's noted that we always hope for the easy fix, the one simple change that will erase the problem in a stroke, but few things in life actually work this way. Instead, success requires making 100 small steps go right one after the other, no slip ups, no goofs, everyone pitching in.

[00:20:42] So I think this is a good summary of how we need to approach this field of medicine. We need to keep working and we need to keep collaborating with our colleagues and with the community to move things forward. And of course, the SRNA has been essential in linking the community and the medical community in this area together. I'd like to thank my colleagues at Johns Hopkins, our talisman, Carlos Pardo, is the leader of the Johns Hopkins Myelitis and Myelopathy Center. And we're very grateful for the support from our community, from the people, the patients we work with, who make our jobs worthwhile every day and from the financial support of philanthropy in the community through Johns Hopkins project, RESTORE, and the Siegel Rare Neuroimmune Association. The support has been essential in many of the developments I have highlighted during this talk, and we hope to continue working for you and for the community over the next few years on this important work. Thank you very much.