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Dr. Wilner:

The International Advisory Committee on Clinical Trials in Multiple Sclerosis has recently updated their 2008 diagnostic guidelines for patients with suspected multiple sclerosis, or MS.

Welcome to *NeuroFrontiers* on ReachMD. I'm your host, Dr. Andrew Wilner. Here to discuss key diagnostic updates and a few red flags from these recently published MS guidelines is Dr. Eoin Flanagan. Dr. Flanagan is the Chair of the Division of Multiple Sclerosis and Autoimmune Neurology at the Mayo Clinic in Rochester, Minnesota.

Dr. Flanagan, welcome to the program.

Dr. Flanagan:

Thanks so much for having me. It's good to be here.

Dr. Wilner:

Before jumping into these updates, Dr. Flanagan, can you tell us which neurological conditions might mimic MS and lead to misdiagnosis?

Dr. Flanagan:

Yeah, I think the first one is that there are many patients out there with common neurologic conditions like migraine, or they may have numbness and tingling or other disorders, and they undergo an MRI of the brain, and they're found to have some white spots within the brain or white matter lesions, and often that leads to the possibility of a diagnosis of multiple sclerosis; but some of those patients don't have the classical symptoms or signs of multiple sclerosis, and they don't have the classical MRI features, and sometimes that can lead to misdiagnosis. So actually, it's more common conditions that are more frequently misdiagnosed. But then there are some new conditions. There's one called MOG antibody-associated disease, or MOGAD, and neuromyelitis optica spectrum disorder, which are diseases that also result in demyelination of the central nervous system and can mimic multiple sclerosis, and those disorders can be diagnosed with a single blood test looking for MOG antibodies or aquaporin-4 antibodies. So there are some new diseases that are different from the prior 2008 guidelines that we really didn't have as much information on at that time or some of them, like the MOG antibody, was not around at that time.

Dr. Wilner:

Ahh, perfect, because that was my next question: What's new, right? What has changed? Why should I read these 2023 guidelines when I know I already read the 2008 guidelines?

Dr. Flanagan:

Well, I think it's been 15 years, and we've had big advances. I work a little bit in the field of autoimmune neurology where we have antibody-associated diseases, and we have discovered probably 20 to 30 new antibody biomarkers, particularly this MOG and aquaporin-4 antibody, which are the most common mimics of multiple sclerosis; but there are other antibody-mediated disorders that are now discovered that can be diagnosed with testing antibodies in the blood or spinal fluid, so that's a real advance that is important that we recognize. And then there are new advances. There are more sophisticated MRI techniques that we can look at. We can look at blood products within the brain. We can better look at different types of sequences that can help us discriminate multiple sclerosis from

other conditions. So I think a lot of advances in many conditions made it important to update these guidelines.

Dr. Wilner:

Oh, thanks for that. So on the one hand, the differential diagnosis has significantly expanded, so we're including new diseases. And let's talk about the other hand, which is how do we better diagnose MS? What can we do better today that we couldn't do 15 years ago?

Dr. Flanagan:

Well, there are some common themes, I suppose, in this that we look at. And some of those themes have not changed quite as much, but it's important to reinforce them—you know, the timing of onset of symptoms. So usually, patients with MS have symptoms that last more than 24 hours, and they come on subacutely rather than very, very quickly or hyperacutely where we might think of a stroke, for example. And then spinal fluid analysis can be helpful looking for oligoclonal bands typical of MS versus other conditions where we often don't see those oligoclonal bands. And then looking at our MRI features can be quite helpful. And looking at our neurologic examination also can be helpful. So some of those, while we have better techniques on the MRI, there are some consistent themes that were still present, but there are still diagnostic errors happening with some of those conditions, so some of those have been reinforced in these guideline.

Dr. Wilner:

What's the gold standard? How do you know if you've made an error or not?

Dr. Flanagan:

The way we diagnose MS, I suppose the way I think about it, is we look at the classical clinical presentation. There are certain syndromes like optic neuritis where a patient will have pain with eye movements, blurred vision, or double vision that are pretty classic for multiple sclerosis; also sensory symptoms like ascending numbness and a feeling like a band all the way down from the waist all the way down to the legs, that's a pretty typical presentation of multiple sclerosis. So we look for that classical clinical syndrome or clinical history, and then we look at our neurologic examination looking for findings that are suggestive of multiple sclerosis like, for example, an internuclear ophthalmoplegia, relative afferent pupillary defect, and upgoing plantar response. Some of those things can help us. And then we're going to look at our MRIs. If the MRI of the brain, cervical, and thoracic spinal cord is completely negative, that will be a big red flag because really you have to be able to see lesions on the MRI. And then we use the spinal fluid also to complement that. 85 percent of people have positive oligoclonal bands. And if you're positive for all of those and everything looks very classic, then sometimes you might need additional tests and you can make the diagnosis of multiple sclerosis, but in other times, it's a bit more nuanced, and maybe not everything is present, or it's in the very early stages or it's a bit more complicated. Then in that situation, we may need to delve into other testing to look at other things, those antibodies I mentioned, the MOG and the aquaporin-4, or we may need to look into other unusual possibilities, be it related to systemic disease. Sometimes rheumatological disorders like lupus or rheumatoid arthritis can involve things in the brain, so sometimes we'll have to look at those things as well. So I suppose it depends on the situation, but our bedrock is the history, the examination, the MRI, and the spinal fluid.

Dr. Wilner:

For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and I'm speaking with Dr. Eoin Flanagan about the updated guidelines on diagnosing suspected multiple sclerosis.

Now, Dr. Flanagan, you mentioned optic neuritis. Could you tell us a little bit more about it? Can you just have optic neuritis and it has nothing to do with MS, or is it always a predecessor to MS?

Dr. Flanagan:

Yeah, MS is one of the common causes of optic neuritis, but there are other causes. As I mentioned earlier, the MOG antibody-associated disease in particular often involves the optic nerve, so that will be a common cause of optic neuritis, particularly in children, or in patients who have recurrent optic neuritis and don't have any other brain lesions, that would be fairly typical for MOG antibody-associated disease. Also, neuromyelitis optica can affect the optic nerve, and often those patients with a MOG and with the neuromyelitis optica spectrum disorder, those patients are often more severe than we see with MS, so a lot of times they're blind in one or both eyes. A lot of times they have both eyes involved, so that can be a clue. And then with the MOG antibody disease, when we look in the back of their eye, we often see a lot of swelling, so that might be a suggestion to move away from multiple sclerosis. And then there are other things like infections. Bartonella infection—it is also called cat scratch disease—can also affect the optic nerve or mimic optic neuritis.

And then it's important to remember that there are other conditions that can affect the optic nerve that are noninflammatory, like a stroke

to the optic nerve. We can have an anterior ischemic optic neuropathy. We can have a patient with migraine headaches who has vision loss that could be mistaken with a headache, and vision loss could be mistaken for optic neuritis, so there are certain other conditions. And then there are structural things or tumors or different things that can have more of a slow progressive course along the optic nerve that would be atypical for MS because most of the time with the MS attacks, it lasts for longer than a day, and usually, it lasts days to a few weeks, and then it reaches its peak, and then it goes down. So if patients are having progressive worsening beyond 21 days with any of these syndromes, then we worry that there might be something else going on.

Dr. Wilner:

You also alluded to symptoms of myelitis. Could you put those in context for us in terms of diagnosing MS?

Dr. Flanagan:

Yeah. So myelitis is a common presentation, and a lot of times patients with MS just have mild symptoms, so they will report that they're numb from their waist down or they have numbness on one side of the body, for example, and in that situation, a lot of times we'll do an MRI, and we'll see some inflammation within the spinal cord. And one of the key features of MS is the length of the lesion, and that can be helpful in the differential diagnosis, so when we look at the MRI, if the lesion that we see on the MRI is less than three vertebral segments, then we think about multiple sclerosis as being the most likely cause, while if it's more than three vertebral segments, there are other conditions that we want to think about—for example, the MOG antibodies or the neuromyelitis optica spectrum disorder. And then when we look on the axial images, we often see that the MS lesions are in the periphery of the cord. It almost looks like a wedge-shaped lesion within the cord, and that can also be a clue because many of those other conditions that aren't MS involve the center of the spinal cord.

And then I'll just mention the speed of onset, again, very important in myelitis. So if a patient has a very severe episode that comes on very quickly, we want to think about a spinal cord stroke, or sometimes functional neurologic disorder related to stressors can do that. And then the other thing is that if a patient has more of a slowly gradually progressive course, then that can be primary progressive MS, which is a different form of MS.

But we also have many other conditions that can cause a progress of myelopathy. There's tumors. Arthritis in the neck, for example, can compress on the spinal cord. There's blood vessel problems. Dural arteriovenous fistula can affect the spinal cord. Sarcoidosis and other inflammatory conditions can affect the spinal cord. So it's really important to look at your MRI and then also to look at the temporal onset of symptoms.

One last thing I'll mention is the pattern of gadolinium enhancement. So we often give contrast when we give an MRI scan, and sometimes the pattern of the contrast enhancement can really help you in distinguishing which diagnosis it is. For example, if you have cervical spondylosis or arthritis in your neck, sometimes there will be a flat band of enhancement called a pancake-like sign, or with sarcoidosis there will sometimes be something called a trident sign where you can have inflammation that forms a trident in the spinal cord on the axial images.

So there are certain clues that we go through in the paper trying to help guide people toward the diagnosis, so I think you can use your MRI to look and see: does it look like MS? And if it doesn't, then what might the diagnosis be, and look out for those patterns that we discussed.

Dr. Wilner:

Well before we close, Dr. Flanagan, do you have any final thoughts you'd like to share with our audience today?

Dr. Flanagan:

Yeah. I'll just mention that the article is divided up into a few different categories. It's optic neuritis, myelitis, brain stem and cerebellum syndromes and cerebral syndromes, and then progressive course. So I think if you have a patient in one of those categories, there are useful tables and figures in the article that you can go to, and it will show you what the red flags are in each one, and then that can help you kind of figure out if you're on the right track with MS, if it looks pretty typical; or if it does not, then you might need to kind of delve in a bit further. There is also a large table with many different features that you can look for, so if you have a patient with certain features that seem atypical to you—maybe they've got a skin rash or they've got something else unusual—if you look in the table, you'll see many of those different features, and that might be a clue to a different diagnosis. So that table is more comprehensive, but it's also quite helpful if you have some sort of atypical feature. If you go look there, you'll see what the most common disease is that cause that.

Dr. Wilner:

That was comprehensive and wonderful. This has been a great discussion about updated guidelines that will help us better diagnose

our patients with MS and related conditions. I'd like to thank my guest, Dr. Eoin Flanagan, for joining me today and for sharing his insights. Dr. Flanagan, it was a pleasure speaking with you.

Dr. Flanagan:

Thanks so much for the opportunity.

Dr. Wilner:

For ReachMD, I'm Dr. Andrew Wilner. To access this and other episodes in our series, visit ReachMD.com/NeuroFrontiers, where you can Be Part of the Knowledge. Thanks for listening.