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Evolving Diagnostic and Prognostic Strategies in Multiple Sclerosis Care

Ashley Baker:
Welcome to *On the Frontlines of Multiple Sclerosis* on ReachMD. I'm your host, Psychiatric Nurse Practitioner Ashley Baker, and joining me to discuss diagnosis and prognosis in multiple sclerosis, or MS, is Dr. Jay Avasarala. He's a Professor in the Department of Neurology and the Director of the Comprehensive Care Center for Multiple Sclerosis and Neuroimmunology at the University of Kentucky.

Dr. Avasarala, thanks for being here today.

Dr. Avasarala:
Thank you for having me.

Ashley Baker:
To start us off, Dr. Avasarala, can you walk us through how the diagnostic criteria for MS have evolved over the past decade?

Dr. Avasarala:
Let's go through some highlights of the 2017 McDonald criteria, and then the more recent 2024. MS, as you know, has always been a disease that we tracked using what are called dissemination in space and time criteria. Space is typically looking at lesions. So, for example, if you take the brain, we typically look for areas of abnormality in specific areas—for example, periventricular, juxtacortical, infratentorial, and then the spinal cord rounds off the fourth area. So we are looking for two areas out of these four to make an inclusion in dissemination in space criteria. Also included in the 2017 criteria were cortical lesions and symptomatic lesions. They could also be counted as part of DIS.

So dissemination in time really is looking for post-gadolinium-enhancing lesions, and simultaneous presence of asymptomatic and symptomatic lesions on MRI on the very first scan also counts towards meeting the dissemination in time criteria, making the diagnosis of multiple sclerosis possible if you eliminate on a parallel basis the mimics. The presence of spinal fluid, abnormalities such as oligoclonal bands—the game has been upped to kappa free light chain assays as well as the more recent findings on CSF that I will allude to. Clinical context is pretty critical, and lesions causing symptoms that can be used to demonstrate DIS and DIT provide the clinical syndrome, which rounds off the diagnostic criteria.

So what has changed in 2024? They have added the inclusion of CSF findings as well as MRI findings, which are divided into central vein sign, being one of the criteria—you have to have more than six lesions if you count them in total across the MRI slices as well as the inclusion of paramagnetic ion rim lesions. When they are present at the outset, then a diagnosis of MS can be made. If all the four locations have lesions, then it becomes MS as well. They've also added the optic nerve as the fifth site. The four anatomical sites that I talked about now includes the optic nerve as another possible area of dissemination in space.

The dissemination in time criteria have been relaxed a bit since they're concentrating on dissemination in space and the kappa free light chain assay has now become equivalent or a substitute for oligoclonal bands. So I think from 2017 up until 2024, the idea was to diagnose MS earlier than it used to be in the past and making sure that they're not making, false diagnosis. So the goal is to avoid false positives, and especially atypical lesions in MS one needs to be careful. But they have expanded the repertoire.

Ashley Baker:
So how do you approach differentiating MS from mimics like neuromyelitis optica or other inflammatory CNS disorders?

Dr. Avasarala:
So NMOSD as well as MOGAD, for example, have serum biomarkers, which are very sensitive and specific. NMOSD has aquaporin-4 antibodies that you could screen for. And in MOGAD, it is the MOG antibodies that you look for in serum. If you do not find them in serum, there is some consensus that you can still look in the CSF, but typically, what you want to test for is the serum.

So MRI findings—NMO shows a periependymal type of a pattern—a longitudinally extensive type of a spinal cord lesion. Instead of being unilateral, it can be bilateral in optic nerve presentation. In MOGAD, for example, it presents much more in children now, with many cases being recognized. It's confluent and it's fluffy on the MRI brain with fully demarcated lesions. ADEM-like features that you see in children are much more common in MOGAD, for example.

Initially, when NMO as a disease was looked at, there were specific criteria like optic neuritis, longitudinally extensive transverse myelitis, and brainstem syndromes, and there are many other clinical presentations in that spectrum, including hypothalamic lesional presentations, and sometimes patients can present with narcolepsy, for example. And so clinical findings are what drives testing, but the testing helps the sensitivity and the specificity of how these diseases are isolated from MS. And sometimes there is still an overlap, and it is challenging to isolate MS from MOGAD or even NMO.

And the other key point I would like to make is when you test for these serum biomarkers, you need to be careful not to initiate steroids in a patient who presents with any of the clinical features suggestive of NMO or MOG because it can skew your results. It can give you a false-negative status.

Ashley Baker:
For those just tuning in, you're listening to *On the Frontlines of Multiple Sclerosis* on ReachMD. I'm Psychiatric Nurse Practitioner Ashley Baker, and I'm speaking with Dr. Jay Avasarala about assessing presentation and progression of MS.

So, Dr. Avasarala, once you make a diagnosis of MS, how do you assess a patient's likely disease course or prognosis?

Dr. Avasarala:
That's highly individualized, but some broad guidelines or goalposts that you would take into account would be sex and age. So if you use the combination of older age and male sex as compared to a cohort that is female and also in the same age group, perhaps the prognosis is worse for the male cohort who are at older age at presentation.

Higher baseline disability—so a patient who comes in perhaps with a spinal cord lesion and has paraplegia, for example, and higher relapses at baseline—that patient might also have a poorer prognosis compared to someone who has a mild case of optic neuritis and has one or two lesions in the brain and maybe some abnormal spinal fluid analysis.

And then also poor recovery between relapses. So someone has the relapse at onset, and then about three months later has another relapse, and then six months later another relapse. So in the first 12 months and first 24 months, relapses and how good the recovery is, is critical.

Smoking, obesity, presence of extensive lesions in the spinal cord, multiple lesions, gadolinium-enhancing lesions, and, of course, early in the disease, you still have to keep in mind there's a component that has probably been en vogue now for maybe 10 to 15 years. It's called PIRA, which is progression independent of relapse activity. So you don't have to have relapses to have progression. This PIRA not only makes it very tough to treat because it doesn't respond well to treatment, but this progression goes on despite what physicians do and occurs in parallel with relapses. It can start pretty early, and it's not as though it is a late phenomenon. It's an early phenomenon. In somebody who has a flare of this PIRA, the physicians know that the trajectory is likely to be off compared to someone who has the classic relapsing-remitting variant. And maybe up to 25 percent of MS patients have this presentation that they come to the physician for, so that has to also be part of the prognostic criteria.

Ashley Baker:
Now, when it comes to treatment planning, how much does the patient's prognosis influence your choice of initial therapy?

Dr. Avasarala:
You need to diagnose them early. MS is like a slow-burning stroke in the sense that axonal losses begin, and it goes undetected. Testing protocols are different between different hospitals in how each person addresses, for example, somebody's limb weakness or optic neuritis. So although we have standardized protocols, I don't think across the country in the emergency departments and wherever we see these patients, even in ophthalmology, general neurology or internal medicine, that these are addressed to bring about a diagnosis quickly.

To answer your question, though, let's argue somebody has a very aggressive disease. Maybe in the last six months, two relapses;

initial relapse was missed; patient did not go or the doctor did not pick up; and now the patient is maybe using a cane in about six months. And then on the MRI, the brain is, as they say, lighting up like a Christmas tree, with multiple lesions. The diagnosis is writing itself. The mimics are all gone.

So, obviously, we use the best tools that we have. The anti-CD20 drugs are what I choose.

Do I use S1P inhibitors or modulators? Yes, I have used them And oral drugs, teriflunomide, fingolimod, ozanimod and other drugs like siponimod—I have used them as second line. It's not as though I don't use them, but I tend to be aggressive very quickly, very early and diagnose early. That's my other aspect that I want the audience to take away. We need to diagnose them early.

Ashley Baker:
That's a great way to round out our discussion. And I want to thank Dr. Jay Avasarala for joining me to discuss diagnostic advances and prognostic tools in MS. Dr. Avasarala, it was great having you on the program.

Dr. Avasarala:
Thank you. Nice to be with you