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Prevention on the Horizon: Early Intervention and Risk Reduction in MS Care

ReachMD Announcer:
You're listening to *On the Frontlines of Multiple Sclerosis* on ReachMD. And now, here's your host, Ashley Baker.

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 potential strategies for multiple sclerosis prevention is Dr. Vikram Bhise, who's a Professor of Pediatrics and Neurology and the Director of the Division of Child Neurology and Neurodevelopmental Disabilities at Rutgers Robert Wood Johnson Medical School. Dr. Bhise, thanks for being here today.

Dr. Bhise:
Thank you for having me.

Ashley Baker:
Well, Dr. Bhise, let's start with the big picture. How would you define prevention in the context of multiple sclerosis care today?

Dr. Bhise:
A lot of things have been upended in our understanding of MS in just the past few years, and so we can think about prevention from potentially even the earliest time points. We now have some information from the 2022 study by Ascherio that showed that EBV—Epstein-Barr virus—is a necessary precursor for MS. So people have now started thinking if you can prevent that process from triggering or even increasing the risk for MS, maybe there's something you can do to prevent the entire disease overall. So that's primary prevention. Plus, we have a number of other risk factors like vitamin D, obesity, and diet. A lot of these things are also now playing a big role.

Maybe we can't catch everybody, but in people who you accidentally catch or who you catch at their earliest time points, we've been using the terms "radiologically isolated syndrome" just on imaging and "clinically isolated syndrome" to mean they've had their first attack and we're not sure yet. If we can best identify which of those folks are going on to have multiple sclerosis, then we might be able to institute prevention at that point, particularly with the early use of medicines.

And then there's people with established MS. So maybe this is a third level of prevention in which we already have the disease in place, and what can we do to minimize the impact and minimize the progression for these individuals by reducing relapses, reducing cognitive changes, and reducing changes on MRIs with new lesions and atrophy? So there's a lot of areas to work on.

So vitamin D, smoking, obesity, and EBV exposure are big areas of investigation right now. And we've also had a lot of work on just time to treatment—making sure that we treat people as early as possible—which is challenging because not every place has access to mid- to high-level efficacy medications. So it's a worldwide goal that is now actively taking place.

For EBV infection, I mentioned that the study in 2022 did a longitudinal evaluation, and it was a great opportunity to examine a huge cohort and focus on just the ones that went on to develop MS. And 800 of those 801 people had an EBV infection—or rather a seroconversion in their lab work—about seven years before, with a range of about two to 15 years. So essentially, getting EBV increased people's risk by over 30-fold, and this is now of great promise for intervention.

Vitamin D became very interesting again. Some of the prior studies had been very mixed. They really didn't show much benefit in supplementing vitamin D. We find that when you check vitamin D levels in MS patients, they're not just low; they're really low. So people

have been on board with trying to see if we can help the disease by supplementing vitamin D—or is it just a marker of poor disease health?

A study just recently published called the D-Lay study tried using high-dose vitamin D—100,000 units every two weeks in people with early MS—and they reported seeing fewer relapses and new lesions on MRI. And so this has sparked the discussion again—maybe we're not using enough. So that's been very exciting.

Ashley Baker:
For those just tuning in, you're listening to *On the Frontlines of Multiple Sclerosis* on ReachMD. I'm your host, Psychiatric Nurse Practitioner Ashley Baker, and I'm speaking with Dr. Vikram Bhise about prevention strategies in multiple sclerosis care.

So, Dr. Bhise, when it comes to identifying high-risk individuals, are there any validated biomarkers or screening tools currently in use or in development that could help us predict MS before clinical symptoms arise?

Dr. Bhise:
Absolutely. There are a lot of biomarkers in play right now. Keep in mind that no single test is definitive. It's really the combination—putting in a careful analysis of MRI, blood markers, and potentially spinal fluid markers, and putting all that information together to risk stratify people and come up with diagnoses that meet criteria.

When you mentioned high-risk individuals, we're also talking about radiologically isolated syndrome, and as I mentioned, that's finding accidentally on an MRI that someone looks like they have MS, but they're telling you, "I'm fine," and that could be a very early time point to intervene. And not just for clinically isolated syndrome and established MS, but the MRI has been a fantastic tool. That's the most important there. But we definitely get benefit from looking at spinal fluid. We test oligoclonal bands, and that's been a validated predictor of converting from RIS and CIS to full MS.

More recently, kappa free light chains have made their way into our latest 2024 diagnostic criteria. They're in some ways similar to oligoclonal bands. Kappa free light chains are produced by your B cells and can be measured in spinal fluid with a test, and we have now cutoffs. The sensitivities and specificities seem very similar to oligoclonal bands, and I've definitely seen people who I was sure had MS, and their oligoclonal bands came back negative, but then the kappa free light chains came back positive. So I started feeling a little bit better that we're definitely on the right track.

Paramagnetic rim lesions are what we call chronic active MS lesions, or as people will say, smoldering. And they're full of microglia that are rich in iron. They're detected with special imaging called susceptibility weighted imaging, or perhaps phase-sensitive MRI. And the presence of these lesions, even in RIS, increases the likelihood of conversion to MS.

Another big finding is the central vein sign, which we've known about for a while. And they've really thought about it carefully and come up with ways to apply it. But if you can look carefully enough, you will see in the MS lesion, which is typically an elliptical spot on the MRI, there's actually a small little vein running through it—a central vein—and if you see this in a majority of the white matter lesions on an MRI, that really favors MS over other things. Other things can have it in low proportion, and that's what makes it a little bit challenging, but having a high amount of it predicts conversion to MS from RIS and CIS.

So a number of these things have now made it into our 2024 MS criteria. And even with people with RIS, they don't have any symptoms, but if your imaging shows just two classic spots plus one more thing, you can get your diagnosis of MS right there just to get on the treatment as early as possible.

Some of the other markers that people have been working on are lesions in the very periphery of the brain—the cortex—so cortical lesions; leptomeningeal enhancement, when the layer outside the brain lights up a little bit; T1 hypointense black holes, although that's better for progression; and brain atrophy metrics. Our brains do atrophy, unfortunately, at a certain age, but it's much faster and earlier, particularly in the thalamus and cortex, in folks with MS. And that can be a predictor for conversion to MS.

And they're now working on trying to take all this information together and say, "Can we come up with a risk score or a predictive model?" There's not one that I think we're all using together now or is highly validated, so that's still a work in progress.

Ashley Baker:
And is there any other ongoing research that could help us better understand MS prevention?

Dr. Bhise:
There is some fantastic stuff going on. One of the biggest things is in EBV. Now that we know that EBV is a necessary precursor, people have really taken a deep look at, can we change the way things are happening for people at high risk? And EBV is a little bit of a notorious virus. We know it's connected to infectious mononucleosis. We know it's connected to Burkitt's lymphoma, Hodgkin's

lymphoma, nasopharyngeal carcinoma, gastric carcinoma, and even post-transplant lymphoproliferative disorder. So it's really connected to a lot of things that would be great to prevent if we could.

So one company, is looking at two mRNA vaccines. These are vaccine programs that are currently underway in phase I and phase II stages. Right now, these studies are focused on adults. There's also another one that's in collaboration with a couple companies in the National Institute of Allergy and Infectious Diseases. It's a gp350-ferritin nanoparticle.

It looks like it's really a labor of love, right? Because where do you really want to do the prevention? Well, probably in teenage or childhood years. But right now, they've got to go through the adults first, so these studies are 18 and up. If they get past that, they're going to move to younger ages. And I think phase B of one of these studies is moving in that direction. But that's what you really want to do, right? And you have to show the safety in adults first before you're going to move to that. The next challenge is, are you going to be able to wait 30 years for MS to develop? Obviously not. So they have to define endpoints of what they're going to be for surrogates, and they're going to have to do these very long registries to follow people.

We also see that there's some new antiviral trials. I believe there's a couple in Australia—the STOP-MS and FIRMS-EBV. They're saying maybe if you use an antiviral to knock down EBV, that can slow some of the MS symptoms, like fatigue.

Another set of really interesting things is looking at health—your general overall health and diet are very important. So now there's very small studies that have been safe. It's hard to say that they're effective right now because they've only got a handful of people enrolled in these studies, but there's ones looking at microbiota transplantation, there's ones looking at probiotics and supplementation, and there's other studies trying to connect all of this together.

The other thing I mentioned—and these studies have already come out—is looking at very early treatment in people with RIS. What if you just start medicine on them right away? And there was the ARISE study, which looked at dimethyl fumarate, and the TERIS study in several European countries in Turkey, which looked at teriflunomide. And they both showed benefit in important risk reductions of over 80 percent and over 70 percent respectively, not just in physical parameters, but also with strong benefit in MRI parameters.

Ashley Baker:
Lastly, Dr. Bhise, what's one takeaway you'd want to share with our audience as we look ahead to a future where MS prevention could become part of standard care?

Dr. Bhise:
I think we're sharing our excitement that we have a lot of information now with EBV, antivirals and vaccines, dietary and gut modification, antiviral therapies, high doses of vitamin D and early use of DMTs, and really making an impact and potentially even longer-term ways of eliminating the disease, ultimately, if possible.

Plus, we've got really great measures now for helping with stratification—not just the MRI and the spinal tap, but also serum markers of neurofilament and other MRI markers that are new with the central vein sign and the paramagnetic rim lesions. So a lot to watch out for in the upcoming future.

Ashley Baker:
That's a great comment for us to think on as we come to the end of today's program. I want to thank my guest, Dr. Vikram Bhise, for joining me to discuss MS prevention. Dr. Bhise, it was great having you on the program.

Dr. Bhise:
Thank you so much.

ReachMD Announcer:
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