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(866) 423-7849

Rethinking Progression in Multiple Sclerosis

Dr. Turck:

This is *Neurofrontiers* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss disease progression and remyelination in multiple sclerosis is Dr. Christopher Lock. Dr. Lock is a Clinical Associate Professor of Neurology at Stanford University in Palo Alto, and he serves as the Clinical Trials Director of the Stanford Multiple Sclerosis and Neuroimmunology Program.

Dr. Lock, we're so glad to have you here today.

Dr. Lock:

Thank you.

Dr. Turck:

Well, set the stage for our discussion a bit, Dr. Lock. When we talk about progression in MS, what do we really mean, and how is it different from the relapses most people are familiar with?

Dr. Lock:

Yes, well, most people have relapsing MS at onset. That's the most common type, where people have episodes of neurologic symptoms, and it's thought that that's caused by areas of inflammation within the brain—focal areas of inflammation. But lately, it's also been recognized that even in early MS, there can be some progression going on in the background, which isn't really understood.

Progression has been recognized for a long time in people who have had MS for a number of years. In older studies, it said that after 10 or 15 years, as many as 50 percent of people may develop some evidence of progression, although in recent years, that number's much lower, with the advent of treatment of the more effective treatment.

So the current generation of medications work very well at suppressing relapses, but it's recognized that they're not as effective for preventing progression. The reason for progression isn't understood, but it's known that when there's active inflammation, as well as damage to the myelin, there can also be damaged to the core of the nerve—the axon—and that can result in progression, because myelin can heal, but when an axon is lost, it can't recover. And also, the demyelinated axons over time are more vulnerable. Oligodendrocytes, the cells that produce the myelin and wrap the axons, provide metabolic support to axons. So, when an axon loses its myelin, it has to work harder.

Axons maintain an electrical gradient, and that's how the action potential works. So the axons have to work harder to maintain that without the myelin. The oligodendrocytes, the myelin-producing cells, also provide metabolic support and energy support to axons. So, over time, the axons can have energy failure and they can have abnormalities in the mitochondria, which are the energy producing parts of the cells, so all those things can contribute to progression or development of disability over time.

So we want to prevent that. There are now 25 or so medications available for treating MS. They're highly effective at suppressing relapses. But, in clinical practice, we still see people who are experiencing progression despite being on those medications.

Often, these are people who've had MS for a number of years. So that's a big area of discussion and focus now. In terms of drug development, people are trying to come up with something to address that part of MS and to develop ways to repair the myelin, because the myelin protects the axons over the longer term, or having something preventing progression or some sort of neuroprotective strategy. So, you can imagine, in the future, people might be on a combination of medications: an anti-inflammatory drug, plus

something to protect the neurons.

Dr. Turck:

So, with that background in mind, let's talk about remyelination. Why is it such a central concept when we think about slowing or preventing progression?

Dr. Lock:

The myelin is thought to be the target of the immune response, and it takes a hit from the immune system. And everyone has a population of cells that make new myelin. There are oligodendrocyte progenitor cells. The oligodendrocytes send out a process that wraps around axons and forms the myelin, which is a many-layered sheet of lipids and proteins around the axon. And it's thought that that's the target of the immune response, and then the axons are injured as a kind of bystander. At least, initially, that's what's thought to be going on.

So there are a pool of cells in the central nervous system, oligodendrocyte progenitor cells. It's something like, I think, five percent of the population of the cells in the brain. And those cells can and do make new myelin. The myelin that's formed is not quite as good as the original. It may be thinner, but those cells can repair the myelin. So if the inflammation is suppressed that's causing MS, that can allow those repair mechanisms to work better.

But none of the existing drugs address that directly. The nerves have to heal themselves, and there are several things required of the oligodendrocyte progenitor cells—they have to differentiate, they have to get to the site of the injury, and then they have to wrap the nerves. So there's several steps involved.

And it's thought, also, that the environment locally is not favorable for remyelination. There are some factors from the inflammatory process. It may prevent remyelination from being as complete as it could be.

Dr. Turck:

For those just tuning in, you're listening to *Neurofrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Christopher Lock about what drives progression and repair in multiple sclerosis.

So, Dr. Lock, now that we've established why remyelination matters, let's explore how it plays out in clinical practice and research. How well can we currently assess or measure remyelination in these settings? And where do you see the biggest gaps?

Dr. Lock:

Yes. That's a key question you raise. I think that's one of the difficulties of that area: measuring remyelination. So one means is the optic nerve, which is more accessible. The optic nerve is an extension of the brain, so it's easier to measure remyelination. So some of the trials have used things like visual evoked potential, so you can measure the speed of conduction through the optic nerve; that's easier to measure. There's optical coherence tomography, which is a method for measuring the thickness of the nerve fiber layer at the back of the eye.

In terms of MRI, people measure the free water fraction. So there's a thing called magnetization transfer ratio. So there's some water that's bound to myelin and some that's free. And MRI array looks at the water molecule protons images, though, so it's possible to design MRI sequences to see how much water is free and how much is burned, and get a measure of remyelination that way.

But I think that's also something that's evolving in parallel. People are trying to figure out better ways of assessing remyelination. Which I think there isn't a lot of, so some of the trials have used the optic nerve people have had optic neuritis and assessing remyelination there.

Dr. Turck:

And coming back to treatment for just a moment, how is our growing understanding of remyelination influencing the way we think about care across different stages of MS?

Dr. Lock:

Well, when people are first diagnosed, that's something I bring up with people, because we talk about the medications and some of the side effects, people say, understandably, they say, “Oh, I don't like the sound of that.” So I would discuss that with them, that the immune response is thought to be against the myelin, but that can also be injury to axons. And, over time, that can lead to accumulation of symptoms or disability.

And, at the present time, there isn't a way to repair the myelin. I think, like most areas of neurology, it's conservation. So, like in stroke, you know that you want to treat people as early as possible to protect the brain. And I think, similarly, the way the McDonald criteria have evolved over time, the diagnosis is earlier and earlier with the idea that the sooner you start treatment, the better, for the protective benefit. So we want to protect the brain as much as we can.

I think from a lifestyle, holistic point of view, it's clearly good to look at all the other things that can be controlled, like diet—being on a heart-healthy, brain-healthy diet, along the Mediterranean diet. And I saw some literature saying how processed foods are probably not good for anyone. They tend to be pro-inflammatory, highly processed food, so healthy diet.

Fixing any comorbidities—what would be considered vascular comorbidities, so things like high blood pressure, high cholesterol, and diabetes. Those are good for everyone to address to protect the brain in the longer term, and that also applies to people with MS. The vessels are living structures. They're not like pipes. So those conditions, untreated, can damage the vessels over time and affect the brain and heart and other organs.

Dr. Turck:

Before we wrap up our program, Dr. Lock, let's look to the future. What should clinicians be watching most closely in this space over the next few years?

Dr. Lock:

There are several different approaches in the pipeline for disease-modifying therapies. We use the monoclonal antibodies a lot these days, in particular the anti-CD20 drugs, which are B cell depleters. The B cells make antibodies, but the effect of those drugs is probably more than that. The B cells also present antigen to T cells. They secrete inflammatory cytokines. It's also thought that B cells can be a reservoir of Epstein-Barr virus, so maybe part of the effect is reducing the pool of cells with EBV.

Antibody drugs don't get into the brain, or only to a very small degree, because they are big molecules that weigh about 150 kilodaltons. The blood-brain barrier doesn't really allow big molecules like that to get through. So people are looking at ways of trying to get treatment into the central nervous system. So small molecule drugs can get into the brain, and they can cross the blood-brain barrier. So there's a lot of interest in those drugs called BTK inhibitors—Bruton's Tyrosine Kinase inhibitors. Those can get into the brain, and they work on the lymphocytes, the B cells, but they also work on another arm of the immune system, the innate immune system, which are cells like microglial cells, which are also thought to be involved in the inflammatory process.

So those look interesting. Also, people are looking at other ways of getting into the brain. For example, CAR T cells—chimeric antigen receptor T cells. So there are trials of those which deplete B cells, like the anti-CD20 molecules, but they can get into the brain and deplete B cells. People talk about compartmentalized inflammation. So it's thought, down the road, some of those immune cells become resident in the brain and they can live in the meninges—the coverings around the brain—and there are follicular lymphoid structures, so the current antibody drugs can't really address that. So things like CAR T cells can get into the brain.

Also, people are looking at ways to try to get the antibodies into the brain. And small molecule drugs can also cross the blood-brain barrier.

Dr. Turck:

Well, with those final thoughts in mind, we come to the end of our discussion. I want to thank my guest, Dr. Christopher Lock, for helping us better understand progression and remyelination in multiple sclerosis.

Dr. Lock, it was great having you on the program.

Dr. Lock:

Thank you very much. Thanks for inviting me.

Dr. Turck:

For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit *Neurofrontiers* on ReachMD.com where you can Be Part of the Knowledge. Thanks for listening.