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Innovations in Diagnosis and Treatment of Multiple Sclerosis

Narrator:

Welcome to Medical Breakthroughs from Penn Medicine: Advancing Medicine Through Precision Diagnostics and Novel Therapies.

Dr. Caudle:

Multiple sclerosis is a notoriously difficult disease to diagnose early on. With no singular confirmatory tests yet available, physicians often become reluctant to identify MS in their patients, leading to years of diagnostic and treatment uncertainty, but new innovations are helping doctors establish earlier diagnoses and start more targeted treatments for MS patients.

On today's program, we're going to explore some of these innovations. You're listening to Medical Breakthroughs from Penn Medicine, and I'm Dr. Jennifer Caudle. Joining me today to talk about MS is Dr. Joseph Berger, professor of neurology at Penn Medicine.

Dr. Berger, welcome to the program.

Dr. Berger:

Thank you, I'm delighted to be here.

Dr. Caudle:

Great, we're happy to have you. So, let's get started. How many people are diagnosed with multiple sclerosis yearly?

Dr. Berger:

So, the estimates are that approximately 10,000 people in the United States are diagnosed annually with multiple sclerosis, and it's been estimated that roughly 400 to 500,000 people in the United States have been labelled with MS. The number, though, is probably an underestimate of the true incidence. We believe that at least 1 in 1000 people has multiple sclerosis, and the reason that we believe that these numbers are underestimates are predicated on a few things, one of which was a study looking at people that applied for disability through the Social Security Administration and had listed multiple sclerosis as the cause of their disability. If one back-calculates the number of people with MS predicated on those numbers alone, it would be far in excess of the 400,000. And then, there is an organization called the Christopher Reeve Foundation, named after the actor who starred in Superman, who started an organization, or his family started an organization that addressed people with spinal cord injury, and if one looks at the number of individuals that are registered with the Christopher Reeve Foundation who have listed MS as the cause of their spinal cord problem, that number, too, leads to a higher estimate than the 400,000 that we see so often repeated. So, many of us believe that the number of individuals is actually significantly higher, and it also appears that the number of people that are being diagnosed with MS has increased over the last decades.

Dr. Caudle:

Okay, well that's very interesting. Can you talk a little bit about gender? Are more women diagnosed with MS than men and, if so, why is this?

Dr. Berger:

So, in short, the answer is yes, more women are diagnosed with MS than men. The frequency is roughly 3 to 1, in some clinics it's closer to 2 to 1 and others it's closer to 4 to 1. Interestingly enough, this disease, multiple sclerosis, was first framed as an entity in the middle of the 1800's by investigators in England and investigators in France, and at that time, through the early 20th century, it was predominantly a disease of men, and somewhere in the middle of the 20th century, there was an inversion and we saw increasing incidence in women, which has continued to climb. So we now see that the disease affects women on average 3 times more often than it does in men. So, the followup

question was, “Well, why is that? Why do we see this disease more often in women than we do in men?” and the bottom line is, we really don’t know the answer to that. Now, it’s not that dissimilar from some other rheumatologic or autoimmune diseases; MS, after all, is an autoimmune disease, it’s just an autoimmune disease that affects the central nervous system, and for many autoimmune diseases, there appears to be a female preponderance. When we fully understand why that occurs, I think we will have a better handle on why it occurs with multiple sclerosis.

Dr. Caudle:

That makes sense. Can you talk about how multiple sclerosis is typically diagnosed and how many providers do patients generally see before they receive a proper diagnosis of MS?

Dr. Berger:

The way that the diagnosis is rendered is on a combination of factors. One, of course, is a history. MS is a disease that is disseminated in time and disseminated in space. What do I mean by that? What I mean is that it can’t be just one area of the nervous system that’s affected; there has to be involvement of more than one area of the nervous system, and that means dissemination in space. The areas that are affected include the optic nerve, the brain and brainstem and the cerebellum and the spinal cord. It is the central nervous system, not the peripheral nervous system that is involved with MS. Now, we will take as evidence of dissemination in space, evidence seen on radiographic imaging. So, many of the lesions that are observed in the brain, and even in the spinal cord, are **inapparent(sic) 5:34** to the patient; they have no clinical symptoms whatsoever and are totally unaware that these lesions had arisen and exist on MRIs of their brain, but we will use that to help us fulfill the criteria of dissemination in space.

The other criteria is dissemination in time. So, everything can’t occur at once, it has to occur over a period of time. Typically, what happens to individuals is that if you were to take somebody who is at high risk for multiple sclerosis and you were to monitor them by doing MRIs at regular intervals—MRIs being magnetic resonance imaging of the brain. If you were to do that before they developed any clinical symptoms, you would see abnormalities developing in the brain, abnormalities of the white matter, a breakdown of the blood-brain barrier initially that is evidenced by contrast enhancing lesions, followed by lesions within the white matter in these areas that occur in the absence of any symptoms whatsoever. So, patients who are diagnosed with multiple sclerosis, with rare exception, have already had the disease going on for a while. It’s difficult to know how long it’s been going on, but typically, it’s been going on for a while and, eventually, one of those lesions occurs in an eloquent area, an area that, when involved, causes a symptom such as a loss of vision due to optic nerve disease or weakness due to a lesion in an area of the brain called the internal capsule or elsewhere where motor

tracks are found. Or, it may cause sensory symptoms; the patient may feel as if they have numbness from the waist down from involvement of the spinal cord, or they may develop problems with their bowel or bladder as a heralding manifestation of their multiple sclerosis.

Now, when an individual has that one event, you'd say, "Well, it'd be very difficult to say that there's dissemination in time on the basis of that one event." However, if you look at the MRI of individuals, you can very often see that lesions are in different stages of evolution, some older, some more acute, and we can now use those parameters to help us diagnose the disease earlier. So, it's not only the clinical picture, the history the patient provides, the physical findings and, of course, one likes to see objective physical findings, not just symptoms, and then objective evidence of disease on the MRI. Sometimes that, in and of itself, is sufficient to make a diagnosis, and we now have criteria that have been refined over the years. The first criteria date back to the 1960s for the diagnosis of MS; those were established so that clinical trials could be done and there be some sort of consistency in who we were diagnosing with MS, and over the ensuing years there has been this dramatic improvement in the quality of the criteria we use. The criteria we currently use are called the McDonald criteria, which incorporate not only the clinical findings, but also paraclinical manifestations, including the MRIs, the spinal fluid, and evoked potentials, which are electrical studies to help us make the diagnosis of MS as early as possible.

So, what we want to see is dissemination in time and dissemination in space, but you may use these paraclinical parameters to establish the diagnosis. And what I mean by paraclinical parameters is largely the magnetic resonance imaging.

Dr. Caudle:

Okay. So, with all of this, what does the future look like for multiple sclerosis patients?

Dr. Berger:

So, the future for multiple sclerosis is very bright. In the early 1990s, the drug beta interferon was released; it was the first drug available for the treatment of relapsing, remitting multiple sclerosis. Before that time, many physicians had a very paternalistic approach to the treatment of multiple sclerosis. In fact, in 1948, at the Association of Nervous and Mental Diseases, two of the most prominent neurologists in the United States—in the world, for that matter—had a discussion on what they tell patients who have MS. One of them said, "I do not tell my patient that they have multiple sclerosis when I know they have it, because when I do, it's vested with lamentable results." In other words, the patient pictures themselves becoming disabled and ultimately dying as a consequence of the disease. And nobody challenged him. One of the other prominent neurologists got up and said, "I

agree with him, that's precisely what I do. If I have to tell anybody about the diagnosis, I tell the family, but I do not tell the patient." That was in the late 1940s, and this paternalistic approach to diagnosing multiple sclerosis existed through the early 1990s until we really had treatment available to us, and that treatment has changed the natural history of the disease. So, in 1993, we had the introduction of the interferons for relapsing, remitting disease. Within 3 years, a drug called glatiramer acetate was released, then there were permutations of the interferons, and in the last decade, we've had oral therapies and infusion therapies, and currently we have 14 treatments that are approved by the FDA for the treatment of relapsing, remitting multiple sclerosis. That is a sea-change from what we had just 2 decades ago, and it has really had a significant impact on the quality of life of patients with multiple sclerosis.

Now, you must bear in mind that this is a capricious illness. What do I mean by that? You cannot predict what's going to happen to a patient who is diagnosed with multiple sclerosis. There are features that may suggest a poor prognosis with the likelihood that they're going to have more disease that may be debilitating, but you can never be absolutely certain of it. In fact, there are statistics that have been derived from autopsy studies carried out in the '50s and early '60s that suggest that as many as 25% of patients that came to autopsy had nothing in their medical records that suggested that they had multiple sclerosis despite the fact that they had pathologically confirmed multiple sclerosis at autopsy. So the disease can be rather quiescent and rather mild, in terms of whatever symptoms people have with it. On the other hand, it could be rapidly debilitating as well, and it can be difficult to be certain as to how a patient is going to do.

So you ask what the future portends; right now we have very effective therapies for the treatment of relapsing, remitting disease. The best evidence suggests that we considerably change the natural history of this disease. There was a recent study looking at the beta interferons, which have been on the market the longest, and what that's demonstrated is that the number of people that have gone on to secondarily progressive disease from relapsing, remitting disease has changed considerably. It used to be thought that within 10 to 15 years, 50% of individuals who have been diagnosed with multiple sclerosis would be wheelchair-bound. That is not the case currently; it is considerably less and, in fact, in this recent analysis of data that had been accumulated over the first 11 years of the use of a beta interferon, less than 5% of individuals had gone on to secondarily progressive disease. So, it appears that we're changing the natural history of the disease. We are very excited about drugs that are on the horizon. There's a whole new class of agents that is administered through infusion that appears to be very safe and not only does this agent, called ocrelizumab, have efficacy in relapsing, remitting disease that appears to be on-par with the most active agents that we currently have, it also appears to have activity against progressive disease. And that, unfortunately, is one of the problems

that we have in the treatment of multiple sclerosis, namely the treatment of progressive MS. So the majority of individuals, 80-85%, have a form of the disease called relapsing, remitting disease. A proportion of those individuals, over time, go on to develop secondarily progressive multiple sclerosis, and about 10-15% of people present with a form of the illness called primary progressive disease. So rather than their illness being punctuated by acute clinical symptoms such as visual loss or weakness on one side or numbness on one side or something along those lines, that ultimately improves and then have a recurrence, a form of the illness we call relapsing, remitting disease, there are these individuals that have progressive disease where the illness slowly progresses day after day, week after week and, unfortunately, the medications that have been available to us to-date have not been very effective or effective at all in treating that form of the disease. But this new medication appears to have efficacy with respect to progressive disease, one of the truly unmet needs for the treatment of MS, and we're very much looking forward to its availability and to the development of other drugs that work for progressive MS.

There is another form of treatment that will be available in the future, I suspect, and that is repair mechanisms, repair strategies for multiple sclerosis. So, individuals that have had multiple sclerosis, have had an attack of multiple sclerosis, have an area of loss of myelin. The myelin is the insulation around nerves, and it is that loss of insulation around the nerve that disrupts the conduction along the nerve and causes the symptom that arises. It doesn't always come back; sometimes that myelin will regenerate, but more often than not, what's left there is a scar, and there are drugs in development currently that facilitate myelin repair, and that, too, is very exciting to us.

Dr. Caudle:

Wonderful. Well, that's all very promising and very exciting.

You're listening to ReachMD and I'm Dr. Jennifer Caudle, host of Medical Breakthroughs from Penn Medicine. Joining me today is Dr. Joseph Berger, professor of neurology.

What are the emerging treatment options for MS, and what advanced treatment options are being provided by Penn?

Dr. Berger:

Well, all of the emerging treatment options that I addressed in the answer to the last question are treatments that have been under study at the University of Pennsylvania in clinical trials that we've been performing, and we continue to enroll patients in these and other trials in an effort to improve the management of individuals with multiple sclerosis and to make their lives better. It's part of what we do as a comprehensive MS center.

Dr. Caudle:

Now, you mentioned that Penn is a comprehensive MS center, why don't we talk about this a bit? Can you tell us what this means, and how is it unique in the spectrum of care for multiple sclerosis?

Dr. Berger:

Penn is designated by the National MS Society as a Comprehensive MS Center of Excellence. In order to be classified as such, one must provide comprehensive care. That means that we have not only physicians that are particularly skilled in managing individuals with multiple sclerosis and other healthcare providers, nurses and nurse practitioners with a skillset for multiple sclerosis, but it is a soup to nuts approach. So, we have, for instance, research programs for patients with MS, clinical trials that they can get into, we have clinicians that are not neurologists who address issues that arise in the MS patient and have familiarity with those particular issues as it pertains to their specialty. So, an individual with multiple sclerosis will very often have a large list of other problems; these include psychiatric issues, these may include urologic problems, gastrointestinal problems, ophthalmologic problems, and in the evaluation of patients for certain drugs, we team up with cardiologists and pulmonologists because of the complications that may arise with some of these drugs, and Penn is an institution where there are individuals in all of these disciplines that have an expertise relevant to the provision of MS care. So, it is truly a team approach in that regard. We have wonderful psychiatry, we have physical therapy and occupational therapy for our patients, we have a social worker embedded in the MS clinic. We have a pharmacist in our clinic—this is quite unique—whose sole purpose is to help patients understand the medicines that they're put on, understand the complications of these medicines, the tests that need to be done, and assist them in getting them on the medicines, which sometimes takes an act of God to start because of insurance issues. So, Penn, in that regard, is truly a comprehensive soup to nuts program for the care and management of patients with multiple sclerosis.

Dr. Caudle:

Wonderful. And as you're talking about this team approach, you've talked about the different clinicians and healthcare providers that are involved in taking care of patients with multiple sclerosis, but as we close, can you really talk about why this team approach to care really is so important?

Dr. Berger:

At the end of the day, what is the reason we exist? We are here to serve. We are here to make people's lives better. So, individuals that have multiple sclerosis very often have not just their neurologic problem, but associated problems that arise because of the neurologic injury that they sustain from the multiple sclerosis. In order to provide the highest quality care possible requires a

team, and we're fortunate that the University of Pennsylvania has a team in order to provide that sort of care.

Dr. Caudle:

Dr. Berger, I'm so glad that you mentioned that. Can you tell us a little bit more about the resources that you have at Penn?

Dr. Berger:

The one thing that I left out is that there are 7 adult neurologists with expertise in multiple sclerosis care, and there are 4 pediatric neurologists at Children's Hospital that are part of our team as well, and that's very unique, and we also have recently established a women's clinic for MS care.

Dr. Caudle:

Well, that's wonderful.

Many thanks to our guest, Dr. Joseph Berger, for joining us today. Thank you so much.

Dr. Berger:

It was my pleasure, I enjoyed it.

Dr. Caudle:

I'm your host, Dr. Jennifer Caudle, and to access this episode and others in this series and to download the ReachMD app, please visit us at ReachMD.com. We encourage you to leave comments and share this program with your colleagues. Thank you for listening.

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