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Rethinking Multiple Sclerosis: A New Biologic Framework for MS Progression

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Hope: Welcome to Practical Neurology: Disease Deep Dive. In this episode, Dr. Daniel Ontaneda, Cleveland Clinic, Cleveland, Ohio, explains why traditional labels such as relapsing-remitting, secondary progressive, and primary progressive multiple sclerosis may not fully reflect the underlying biology of the disease and why a more dynamic framework could better capture how MS changes over time.

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Joe Rusko: Hello, everyone. I'm Joe Rusko, Editor-in-Chief of Practical Neurology, and I'm here with Dr. Ontaneda today. Dr. Ontaneda, please introduce yourself and tell us a little bit about your role at Cleveland Clinic.

[00:00:45]

Daniel Ontaneda, MD, PhD: Thanks so much. My name is Daniel Ontaneda. I'm a professor of neurology and a neurologist at the Mellen Center for Multiple Sclerosis Treatment and Research, where I also am the director of research.

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Joe Rusko: Thank you. So, my first question is, neurologists are increasingly seeing patients whose relapses and MRI activity appear to be well controlled, at least according to those measurements, yet they continue to accumulate disability. What have we learned about the biology of MS recently that helps explain that disconnect?

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Daniel Ontaneda, MD, PhD: That's a great question, and I think it's a clinical scenario that I think many people who see individuals with MS in clinical practice, either neurologists or nurse practitioners, may identify quite easily with. And that is the patient who might be on a disease-modifying therapy. It could be a high or moderate efficacy medication or even what we consider a modestly effective disease-modifying therapy.

And you are typically monitoring through MRI, and that MRI doesn't show any new lesions. It's not showing any inflammatory disease activity, so no gadolinium enhancement, no T2 lesions, and no enlarging lesions either. And despite that relative stability in terms of the MRI and despite the fact that the patient might say, "I don't have any attacks or relapses in the last, say, twelve months," they do describe a slow worsening of function.

And that slow worsening of function can manifest in many different ways. Prototypically, when we think about that, we assign that a label of progression of disease, and we think about gait difficulties or ambulation difficulties, but I wouldn't limit its scope to just motor worsening.

I think we now think about it a bit more broadly. We think about it as worsening in fatigue, for example, or worsening in cognitive function, worsening in hand function or could also be worsening in balance coordination. And some of these are clearer on our neurological exam, some of them are more difficult, and some of them are just how people report their symptoms.

So that's something that we've realized we probably have to increase our scope of what we consider worsening. And I think one of the most important developments in our field is that we recognize that this is something that can occur across the spectrum of multiple sclerosis. So there was a historical knowledge that said that that type of progression typically happened later in the disease when a

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person had had relapsing-remitting multiple sclerosis for many, many years.

And now what research has shown us is that that slow worsening of function can occur from relatively early in the disease in people that have their disease activity controlled. We have been able to discover this mainly because in the past, if we didn't have medications that completely controlled relapses or attacks, we assumed that some of that worsening was related to the presence of those attacks or those new lesions.

Now that we have relatively efficacious medications that abrogate attacks and relapses and new lesions, now we're seeing that that progression can occur actually from relatively early in the disease, that worsening can occur from relatively early in the disease.

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Joe Rusko: And is that why biomarkers are increasingly important for progression?

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Daniel Ontaneda, MD, PhD: I think so. Our field has benefited from the presence of really good biomarkers for the inflammatory aspects of multiple sclerosis, and specifically the focal inflammatory aspects of multiple sclerosis.

So, the stuff that relates to relapses and attacks, and those are new T2 lesions and gadolinium-enhancing lesions. Those are great biomarkers, and there's emerging data that neurofilament light is a great biomarker for that as well. And what those measures allow us to do is to predict if a person is going to have a relapse or not.

For that slow worsening of disease, we don't have great biomarkers. And the reality is that we wait for them to develop to call them. But it would be great if, for example, we had biomarkers that might be a little bit more sensitive, that might predict when this is going to happen before a person experiences worsening.

Several candidates exist. I would say none of them are truly validated. We've thought a lot about progressive loss of brain volume as a potential candidate for that. We've thought of measures coming from the spinal cord, spinal cord volume potentially working for that. And we've also thought about optical coherence tomography measures as potential measures for that.

And then finally, blood biomarkers, and I think the one that people associate the most with that slower worsening progression is something called GFAP. So, I think those are all candidate biomarkers. I don't think we know or we haven't identified one that is perfect at predicting this.

But I think it's a matter of generating the data, looking for the biomarkers. And perhaps I'm moving towards a feeling that progression is a little bit complicated, and that worsening is a little bit complicated. It's not just one mechanism, right?

It probably is a combination of mechanisms, and therefore, if you think about a biomarker, it probably won't be a single biomarker. It'll probably be a panel of biomarkers that might be able to predict.

[00:06:06]

Joe Rusko: Thank you. So want to talk about the International Roadmap, you are a collaborator on this project, and it proposed a more biologically informed description of MS.

Does that work suggest that these labels, so relapsing, remitting, progressive MS, they sometimes obscure what's happening biologically because it's not a hard and fast definition?

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Daniel Ontaneda, MD, PhD: Yeah, I think so. I think the labels were created based on clinical observation of patients many years ago.

And they helped our field. They helped identify, to an extent, who would benefit from these anti-inflammatory treatments, which was beneficial. But I think we've recognized now for some time that these boxes of how we catalog multiple sclerosis are probably not really fit for purpose.

And they're not fit for purpose because rarely in biology do you see clear demarcations between pathological processes. What we have learned and what we have understood is that there's different processes that are ongoing in multiple sclerosis, and those processes can vary over time, and those processes can change in a single individual.

And so, our previous labels were really about identifying individuals, and many times once somebody was called secondary progressive MS, that was it. You couldn't change or you couldn't go back when many times people might not have ongoing progression. They might have progression for a while, and then it stops.

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And so, what do you do with that scenario? And similarly, relapsing-remitting is a label that we've used a lot but sometimes doesn't sit perfectly with patients. When we say relapsing-remitting, we mean there's periods of attacks and periods where there's no attacks. But if you talk to a person with MS, they will tell you that, rarely do all of their symptoms completely remit.

So, it's not probably a fit description for the condition itself. And then finally, I think philosophically there was a tendency, this was present a little bit more some years ago, to think about whether different disease courses of multiple sclerosis were different conditions somehow, that they were separate entities.

And that especially happened when you thought about relapsing-remitting versus primary progressive MS. Those are individuals who typically don't have attacks. And I think one of the things that we really wanted to do with this new roadmap is dispel the notion that they're separate diseases.

And so, we are entering a new framework here, and the framework is that multiple sclerosis is a single disease, and that single disease can manifest in different ways. And those manifestations can change over the time course and over the lifetime of an individual. And as far as we know, we recognize two main processes.

One is attacks, and attacks are related to acute focal inflammation, and the other process is slow worsening of disability that is accrued independent of relapses. And we think that that obeys probably a host and a variety of different pathological mechanisms, including perhaps neurodegeneration, perhaps chronic inflammation, perhaps energetic failure of neuronal cells.

And although we haven't been able to perfectly map out exactly how each one of those contributes and where they contribute, I think it will help us as a field to think about these processes separately. And I think one of the things that we've tried to do is to understand also that there are certain modifiers that relate to these processes.

So, it's not just that you have MS, and you're going to go along your course, but you have MS, and then there are treatment effects of disease-modifying therapies. Then there are, of course, things that might influence how the disease is progressing and that includes different social, socioeconomic factors, comorbidities.

All these things that I think when we think about a patient, we put that all in our head, right? And we try to make sense of that when we're seeing patients, and I think patients realize this as well. And so, trying to have an approach where, as a field, we can agree on how we should classify the disease course is really healthy.

One of the key things is that we want to base it on what are the different biologies that are present in multiple sclerosis. And this follows along what has been done for many other neurological diseases with Alzheimer disease and Parkinson disease being clear examples of how you let your knowledge and the biology help you interpret what is happening clinically in an individual.

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Joe Rusko: What has been the reception so far to the roadmap? I'm curious about how your colleagues are thinking about this topic.

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Daniel Ontaneda, MD, PhD: I think it's natural whenever you change a framework of how we approach a disease, I think there's going to be some hesitation. Personally, I think what I've experienced the most in speaking with colleagues is that one of the things that people are worried about is how our regulatory bodies that approve medications will handle this information.

So, we say multiple sclerosis is a single disease, and you could have a relapse component to it or relapse biology, if you like, and you could have a worsening biology associated with it. And that might vary, and they might be present at the same time together. The problem is that in our current framework, medications are approved based on the old labels.

So regulatory bodies have traditionally approved medications for relapsing-remitting multiple sclerosis or for primary progressive or for secondary progressive MS. And my response to that is that the regulators, I think, are happy if we come to them, and they told us this at the meeting, that, "If you come to us with a remapped disease framework, as long as there's agreement in your field, we're happy to support that."

And I think they're open to that. And we already got some indication that the FDA was already thinking in this way, specifically when, historically, our medications were approved for relapsing-remitting multiple sclerosis, and then a trial was done where a medication that was an anti-inflammatory helped individuals with secondary progressive MS who had disease activity.

The FDA took that one trial and basically said, "All medications for relapsing-remitting, as long as there's inflammation, are approved for use, even if it's secondary progressive MS." And so that signals that there is the understanding that the biology is really what's driving the treatment response,

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I think the other somewhat complicated issue, and this one's probably one that's going to be a little bit more difficult to tackle, is that while we understand the biology of acute focal lesions and relapses quite well, we as a field don't have as much of a handle on progression and slow worsening of the disease.

And the reality is that there's probably several biological processes, and they can overlap. And how to quantify those in terms of your biomarkers and in terms of the clinical behavior of individual is a little bit tricky, one, because we don't understand it, and two, because there's a lot of different measures.

And so, trying to pin all those measures into a single summary level, abbreviation of what a person's MS looks like is going to be, I think, that's naturally going to be a little bit hard. And so, we're going to have to have some way of dealing with that complexity and distilling it to something that is useful to clinicians but also is useful to people with MS and caregivers.

And so, we recognize that, how we call our disease course and our disease course framework has to be something that is widely usable and applicable. And I think in there lies a little bit of challenge with the complexity that we're dealing with.

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Joe Rusko: So, the hypothetical patient who had no relapses and no obvious new MRI lesions but they're walking more slowly, worsening cognition, and how the neurologist can determine whether that would represent MS progression under your new framework.

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Daniel Ontaneda, MD, PhD: I think the one thing that I think we like to identify is make sure that you treat what you can treat, which is inflammation, right? So, you want to make sure that a person is not having new lesions and is not having attacks, and you've controlled inflammation.

And if you've done that, and you identify an individual who continues to worsen, I think one of the things I would like to highlight is, we shouldn't think narrowly here. I think the individual who has had MS for 35 years and their walking is slowing down and over the course of the last year has started using a cane or has then transitioned to a walker, I think if you ask the majority of neurologists, they would accurately describe that as worsening of the disease.

And probably some progressive component of multiple sclerosis. I think where it's a little bit harder is in the individuals who, their gait is intact, they're walking independently, but they might have slow worsening of cognitive function that you might be able to document on your psychological testing.

That might be a little bit harder to do for a neurologist, but I think just as important. And then I think one of the things that we reflected on when we're thinking about this new disease course framework is that the opinion of the patient is something that we use a lot as neurologists.

And many people in the room said, "Well, I can tell if my patient has progression because they tell me. They tell me that something is worse." And I think that description of the patient, I think is important, and we need to be a little bit better of capturing that in something called patient-reported outcomes and creating some threshold for what we consider a meaningful change in a patient-reported outcome. That issue with patient-reported outcomes is that sometimes there's a little bit of noise associated with them. Because, if you ask me how I'm doing today versus how I'm doing tomorrow, it might be different, and I don't have MS, and we know there's a lot of variability in MS.

And so, we want to try to kind of work out what are normal day-to-day fluctuations and not misinterpreting that as progression, and what is truly a sustained true worsening of function that is reflected in a patient-reported outcome. So those are all challenges that lie ahead.

And I think they're challenges that other conditions have dealt with as well, and they've been able to actually make some advances in. So, I'm confident that our field can integrate these measures better.

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Joe Rusko: So, it sounds like you're arguing for more biomarkers, more defining and this new framework, but aren't you also indicating that there needs to be a different treatment approach as well? So, looking at not only stopping lesions and disease progression, but some of these co-factors as well—cognition, fatigue, things like that.

Daniel Ontaneda, MD, PhD: I think you're right in the sense that, certainly the purpose of redefining this in a sense is to try to identify better therapies. Ultimately, what we strive to do as neurologists for all our patients, and what we strive to do as researchers is to give people solutions to issues that are brought on by multiple sclerosis.

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I think one of the important things about thinking about the biology is, we have great treatments for relapses, we have great treatments for acute lesions. We don't have as many treatments for purely progressive MS. There is currently one therapy that was approved in Europe for progressive forms of multiple sclerosis, which is great news.

But I think, as I highlighted before, many different mechanisms are at play. So, I think underpinning all of this is our desire to develop better therapies. And the reality is, in progressive MS, you're probably going to have to develop therapies that target specific biological mechanisms.

So, you're probably going to want a therapy that hits on chronic inflammation. You might want a therapy that is a primary neuroprotectant medication. You may want a therapy that is perhaps an energy metabolism, a savior for axons and neurons. And so, the idea here is that if we have the ability to classify these biomarkers and identify them in individuals, it can lead us to selecting the right type of patients for the right type of mechanisms, for the right type of drugs, for the right type of clinical trial.

So, when we think about this, I think we always try to take evidence from other areas that have been huge successes. And I think one of the success areas, for example, we can think about is oncology. And oncology really profiles their patient, and the type of tumor people have, and they target therapies to very specific mechanisms that relate to perhaps the genetics of the tumor.

In multiple sclerosis the parallel would be, it is certainly not a single cell disease. This is a disease that is a combination of things. But the idea is that if you have a person who's worsening and that worsening might be driven, for example, by chronic inflammation, you could target that within a medication that targets a chronic inflammatory response.

Or if you think that it's more something that's more on the energetic side or more on the neurodegeneration side, you could target those individually. So, I think the hope is that if we translate these biological disease course measures with biomarkers, it will allow us to design better clinical trials.

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Joe Rusko: So, what's next in terms of developing the framework, disseminating it, and then refining that?

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Daniel Ontaneda, MD, PhD: Some of this work is still ongoing through the International Advisory Committee for Clinical Trials in Multiple Sclerosis.

And over the course of this year, we've had virtual meetings every several months that are focusing on the different measurements that we can use in clinical practice. So far, we've had virtual workshops that have focused on patient-reported outcomes. We've had virtual workshops that have focused on specifically clinician-reported outcomes, so these are the measures that we use, like the MSFC, Multiple Sclerosis Functional Composite.

And we've had one that focuses on imaging markers that describe the disease course. And our last one that's still pending is one that's working on biomarkers, specifically fluid biomarkers. And our idea is towards the end of the year to have a meeting and put that knowledge together and get some agreement on what are the measures that we think are appropriate to include in disease course descriptors.

And so, it's an iterative process. First, we identify what measures do we need, what measures can we agree on, and then hopefully in the future, what we're going to be doing is saying, "Well, how do we take those measures, and how do we construct them into a disease course that makes sense?"

That's the second stage step. So similar to how we've spent a year working on the measures, I think we're probably going to have to spend at least a year also on how to puzzle those together in a way that makes sense and also taking into consideration what are the modifiers. Like we talked about, modifiers from a comorbidity status, a modifier from a disease treatment status, a modifier from a socioeconomic perspective, that are all going to be really important.

I think that's going to be challenging work to do; hopefully, we can arrive at something that is going to be useful. I certainly can say that, whatever we arrive at, I think it'll be an improvement compared to what we have now, which is three boxes that really don't describe very much.

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Joe Rusko: That's great.

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Daniel Ontaneda, MD, PhD: Yeah.

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Joe Rusko: Thank you for your time today, Dr. Ontaneda. We appreciate your insights.

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Daniel Ontaneda, MD, PhD: And thanks so much for having me. It was a pleasure to discuss these fascinating topics.

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Hope: Thank you to Dr. Ontaneda for his insights in this episode of Practical Neurology: Disease Deep Dive. And thanks to you, our listeners. This podcast is brought to you by the editors of Practical Neurology. Be sure to check out practicalneurology.com for more episodes in the field of neurology.

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