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Advancing MS Care with Multimodal Aging Signatures and Proteomic Biomarkers

ReachMD Announcer:
You're listening to *NeuroFrontiers* on ReachMD. And now, here's your host, Ryan Quigley.

Ryan:
Welcome to *NeuroFrontiers* on ReachMD. I'm Ryan Quigley, and today, I'm joined by Mr. Dylan Hamitouche and Dr. Adil Harroud, who recently presented research on multimodal aging signatures and proteomic biomarkers in multiple sclerosis at the 2026 ACTRIMS Forum. Mr. Hamitouche is a medical student at McGill University in Montreal.

Mr. Hamitouche, thank you so much for doing this. Really appreciate you taking the time to join us today.

Mr. Hamitouche:
Thank you, Ryan. It's a pleasure to be here and to discuss this with you.

Ryan:
And Dr. Harroud is a neurologist and the co-leader of the Neuroimmunology Diseases Research Group at the Montreal Neurological Institute at McGill University.

Dr. Harroud, thank you for being here.

Dr. Harroud:
Thank you for having us. It's our pleasure.

Ryan:
Dylan, to start with you, what initially motivated you to look at MS through the lens of aging signatures?

Mr. Hamitouche:
We know from the literature that aging is the most important factor for prognosis in MS and that it drives disability independently of what MS subtype you have at the onset of the disease. But the issue with aging is that it's very heterogeneous across people, and it varies between different individuals. So, if you have two people who are both 50 years old, there's probably going to be one that looks a bit older than the other. And the reason is that aging is driven by complex biological processes at the cellular and subcellular levels.

So, what we aimed to do was study aging through the lens of biological processes using proteomics, MRI data, and telomeres to be able to define aging at a biological level and then see if biological aging can predict MS susceptibility, outcomes, and even mortality.

Dr. Harroud:
And I'll just add on, as many of your listeners will know, MS has gone through a real revolution over the past decade where we have gone from a disease that was basically untreatable to a disease that is now highly treatable with very high efficacy treatments—very effective therapies that can pretty much shut down one of the dimensions of the disease, which is the inflammatory attacks that bring on neurological disability, sometimes temporarily, and sometimes, unfortunately, in a permanent manner.

But what we have not solved yet is that with these individuals, even when we stop their relapses, some of them still get worse, and the drivers of that progression are not very well understood. But it correlates so well with aging, as Dylan just explained, that aging processes probably explain a substantial component of this.

Ryan:
Thank you very much for that. Now, Dr. Harroud, could you dive in a little bit into the methodology behind this study?

Dr. Harroud:
So, to perform this study, we leveraged a wonderful resource called the UK Biobank. This is a large prospective cohort that follows half a million people from the United Kingdom and has a large dataset that consists of clinical variables as well as multiomics. And a subset of that study, about 50,000 people, had high throughput proteomics performed such that for every one of these 50,000 participants, we had measurements for about 3,000 proteins from the blood. This allows us to then ask which of these proteins best correlates with aging and can best explain differences in age.

So, to do that, we built a machine learning model that was able to select the appropriate proteins among these 3,000 and then develop a prediction for biological aging that we can then compare to the individual's chronological age. And what we obtain in comparing those two is a gap where some individuals will be biologically older than their stated age, and some individuals will be younger. Then, we can incorporate these predictions into models that compare people with MS to people without MS and also compare outcomes among people with MS.

We had access to additional measures of biological aging. We know that proteomics is not the only way to measure this. We also had access to telomere length, which gets shorter as people age. And we also developed a very similar model for brain MRI where we trained, again, a machine learning model that predicts age on the basis of an individual's brain MRI scan. And that allows us to have multimodal characterization of biological aging across proteins, neuroimaging, and telomere length.

Ryan:
Now, Dylan, turning back to you, what stood out to you most in terms of findings from this study?

Mr. Hamitouche:
Well, there's a lot of things to discuss here. First of all, we were able to accurately predict biological aging using different markers - so proteomics, and then also MRI. And we found that some of these metrics were accelerated in MS. So, for example, people with MS had accelerated global proteomic aging, brain-specific proteomic aging, and brain MRI aging. Interestingly, these metrics were not correlating well in the control group, but these correlations got stronger in the MS group, suggesting that there could be a convergence of structural and molecular aging in MS.

Something also that is super interesting is that because the UK Biobank is a prospective cohort, we're able to find that brain aging started accelerating 11 years before the diagnosis of MS.

And finally, I'll say, relating to mortality, that each one-year increase in the brain age gap- the difference between the brain age and the age determined by the date of birth- increased mortality by more than 50 percent. And this is huge considering that people with MS were 2.5 years older than controls when looking at it through the lens of brain aging.

Ryan:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Ryan Quigley, and I'm speaking with Mr. Dylan Hamitouche and Dr. Adil Harroud about their research on multimodal aging signatures and proteomic biomarkers in MS.

So, Dr. Harroud, given your findings, what's the potential value of identifying proteomic biomarkers that reflect aging related processes in MS?

Dr. Harroud:
One of the major challenges with MS is that it can be quite unpredictable, and that has a substantial impact on the lives of people with MS. What we saw through this study is that increased proteomic aging correlated fairly well with a number of physical, cognitive, and radiological outcomes. Perhaps this is a model that we can use to better prognosticate and better understand who is at greatest risk of worsening in the future. We are always in search of biomarkers that can be as dynamic as proteins are so that we can perhaps use them to understand treatment effects.

There is a huge unmet need in addressing progression in multiple sclerosis, and one of the challenges is that it's very hard to know if a drug works or doesn't outside of conventional clinical outcomes, which tend to be noisy and require very large sample sizes. And so if we are able to identify good biomarkers that correlate with disability and that can potentially be dynamic, then we may be able to test the effects of interventions on a smaller scale in phase 2 studies prior to moving to large-scale clinical studies.

Ryan:
So, Dylan, turning back to you now, what are some of the key limitations or unanswered questions from this work?

Mr. Hamitouche:
I'll say that the UK Biobank is a cross-sectional study, and even though the prospective design was really interesting, it would be very

good to replicate this in a longitudinal study with repeated measurements. We're actually working on this at the moment to see how biological aging can reflect relapses and responses to disease-modifying therapies, and also if we could use biological aging as a clinical biomarker.

I'll also say that the UK Biobank, the dataset that we use, is an older cohort from 40 years old to 70 years old, and it would be interesting to see if this can be applied in a younger cohort and even in pediatric MS.

Ryan:
And finally, Dr. Harroud, to close us out here, how do you see this study contributing to the broader conversation around more personalized care for patients with MS?

Dr. Harroud:
Well, we see that in MS, there are different biologies at play, not only between patients, but even within an individual patient. In some phases of the disease, there is a relapsing biology that is predominant, and those individuals need effective anti-inflammatory therapy to be able to control that. But then, within the same individual, there may emerge over time a greater progression biology where different mechanisms take over, and their increased immunosuppression doesn't always lead to clinical benefit.

So, we need to acquire sufficient tools to be able to interrogate these different dimensions. Currently, with neuroimaging, brain MRIs, and spinal cord MRIs, we have a good measure of some of the lesional aspects of multiple sclerosis, but we don't have good measures yet for the biology of progression. And we do see, as we mentioned at the beginning, that it is strongly associated with aging.

So, being able to start to dissect out these components that relate to organ-specific and whole-body aging becomes really interesting in understanding what is driving disability in an individual patient and being able to potentially tailor treatments to what is driving that disability.

Ryan:
That's a great look ahead as we come to the end of today's program. And I want to thank my guests, Mr. Dylan Hamitouche and Dr. Adil Harroud, for joining me to discuss how multimodal aging signatures can help us identify proteomic biomarkers in MS.

Mr. Hamitouche, Dr. Harroud, it was great having you both on the program.

Mr. Hamitouche:
Thank you, Ryan. It was a pleasure being here.

Dr. Harroud:
Thank you for having us.

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