Ruth Adewuya, MD (host):

Hello, you are listening to Stanford Medcast, Stanford CMEs podcast, where we bring you insights from the world's leading physicians and scientists. This podcast is available on Apple Podcast, Amazon Music, Spotify, Google Podcasts, and Stitcher. If you're new here, consider subscribing to listen to more free episodes coming your way. I am your host, Dr. Ruth Adewuya. This episode is part of our Hot Topics Mini Series, and is supported in part by an unrestricted educational grant from Novartis Pharmaceuticals Corporation. In the last MS episode, I chatted with Dr. Lauren Steinman on the role of the Epstein-Barr virus in MS, its impact and potential opportunities for treatment. In this episode, I will be chatting with Dr. Emmanuelle Waubant on the gut microbiome in MS. Dr. Waubant is a neurologist who specializes in treating patients with MS. She serves as the director of the UCSF Regional Pediatric Multiple Sclerosis Center.

Ruth Adewuya, MD (host):

And her research focuses on new treatments for multiples sclerosis. She serves on the clinical care committee of the National Multiple's Sclerosis Society's local chapter and the translational research review committee for the society's national office. A prominent contributor to scientific journals in her field, Dr. Waubant is one of the two chief editors of Multiple Sclerosis and Related Disorders. She is the MS section editor for Annals of Clinical and Translational Neurology. Thank you so much for chatting with me today. I think a great place for us to start would be to understand your interest in neurology as a subspecialty and multiple sclerosis. What's your journey towards this focus?

Emmanuelle Waubant, MD (guest speaker):

My journey towards neurology was a very short journey. As soon as I started medical school, when I was in my second year of medical school, when we started studying the physiology or the nervous system, I had this aha moment, I was just going, "Wow, this is so cool. This is complex, yes, but this is so cool." Because of all the different pathways and what they did and the control of different parts of the body, I found it completely fascinating. So that was it for me. I wanted to be a neurologist from very early on. And then when I started to study, actually it was even before I was a resident, in France you have to take a qualifying national exam to be ranked and be allowed to specialize. And if you are well ranked, you can choose your specialty. And if you don't, then you take what has not been taken.

Emmanuelle Waubant, MD (guest speaker):

And to study for that qualifying exam, we had to study pre-comprehensively not only neurology, but also immunology and other specialties, and the immunology was something that also I found fascinating. And that was some years ago, and I have to say, the immunology has become even much more complex in terms of our understanding of the different relationships between different cells, between cytokines and chemokines and so on and to receptors, and so when I started neurology, I was already interested in MS. And the crossroad between neurology and immunology, there's few diseases, and that includes MS. And I think MS is a disease that's common enough that you could really become an expert almost full time because you can care for many patients affected by the disease. And what's been exciting is that over the past 20 years is probably the field of MS that has changed the most dramatically in terms of coming up with different treatments that really benefit patients who have MS. I don't regret becoming an MS doctor.

Ruth Adewuya, MD (host):

That's fantastic. I like what you said that it seems like there's a lot of excitement in this field and a lot has been done. How did you become interested in researching the role of the gut microbiome in MS?

Emmanuelle Waubant, MD (guest speaker):

I think that when I started to look at that was over 10 years ago, and the interest grew out of reports, first in the immunology world, showing that the microbiome could possibly modulate the immune response, and then people have started to work with animal models. And I think that one of the first group that did that was a group of Lloyd, Casper, and they were able to actually induce EAE, which is a model of MS in the animal model, basically modulating the gut microbiome either by having the animals in a sterile environment or not, they could modulate the rate of the disease, and then they could modulate further the disease using different portion of bacteria of interest, and also modulating with antibiotics. So from that time on, I think it became very clear that it was something that definitely would have to be studied in MS.

Emmanuelle Waubant, MD (guest speaker):

The very first report that I found was fascinating was from the early 90s from [inaudible 00:05:22] group, her group actually reported that in minors prone to develop MS, those that were raised in a completely sterile environment were actually not developing the disease, whereas the ones that were fed and their usual feed not necessarily sterile and were raised in a non-sterile environment were developing the disease. So already back then, there was some hints that possibly bacteria or viruses in the environment could modulate the risk of EAE. But I think it was forgotten for many years and it's really the beginning of the 2000, 2005 years that people rediscovered that because it was starting to be studied in other fields of medicine.

Ruth Adewuya, MD (host):

That's really intriguing. The interest came from some of the seminal work in this area, and that's what got you into it to move that conversation forward. So as you look back at your research and the work that you've been doing, what have been some of those significant findings?

Emmanuelle Waubant, MD (guest speaker):

There's two different things. Some of the research I'm involved in is running clinical trials and trying to identify promising medications for patients. I would say that from my own investigator led initiatives, I think that one of the study we had done with my colleague, Scott Zamvil, at UCSF was actually to look at atorvastatin in very early phases of MS. And the study was negative, but we could detect that the MRI level trend towards lowering the accumulation of new MS lesions. And it's interesting that later there's another group in England that actually identified possibly slowing down of brain atrophy and is completing currently a study with that treatment strategy, so that's for clinical trials. And then I've done a lot of research also with epidemiology, so risk factors for MS but also risk factors in the environments that may modulate the risk of having exacerbations or new scars and so on. And that's where the microbiome and diets and so on fit in.

Ruth Adewuya, MD (host):

Exactly. And that's a great lead into my next question, because I think the big question that I found doing my research for this conversation is what is the cause or the consequence. Can you help clarify is altered gut microbiota a cause or a consequence of MS?

Emmanuelle Waubant, MD (guest speaker):

The big picture is that I think at this point we really don't have enough argument to say that the changes that have been identified in patients with MS are actually the cause of the disease. And the reason for that is when you study MS, typically you have to wait for the clinical onset of the disease before you can start collecting samples, because you can't guess who is going to develop the disease. With some other disorders, you actually can identify much more clearly patients at risk. And for example, people have looked at the gut microbiome in babies born from a mother who had a high risk of asthma. And so you do a short study in many babies, but the study doesn't have to last for very long, and you can collect samples from birth on for six or 12 months and then you can have your answer whether there's really an abnormality in the microbiome that precedes the onset of the disease.

Emmanuelle Waubant, MD (guest speaker):

For MS, it's much more difficult because, first, although they are some patients we know may be at risk of developing MS, this increased risk is actually small enough that it would take literally tens of thousands of individuals to be monitored that way before a few develop MS. The second thing is that we know that MS very often is preceded by pretty long purely biological phase. And by that, I mean we know that patients may have five years, 10 years, on average, they will be developing lesions on their MRI if we were scanning them. And then it takes five years or 10 years before they develop the first symptoms of the disease. So the patients who end up having had MRIs before the onset of MS, most of the time is because the MRI was done for something else, they were in a car accident, they had a concussion, or they had really pretty severe headaches and so they did an MRI to find out if there was something that was explaining the headaches and so on.

Emmanuelle Waubant, MD (guest speaker):

But we know that there's this silent clinical time that precedes the clinical onset. And which means that even if we're able to get samples a year before, this is onset, we may still be well past the biological onset of the disease, so it makes it really challenging. And I think in the field of neurology, all the neurodegenerative diseases, whether we're talking about Parkinson's or Alzheimer's disease and so on, we are all facing a little bit of the same in terms of trying to get samples really as close as we can to a biological initiation of the disease. So as a result of these long, silent, hidden phase of the disease, most of the studies that have been published are actually studies that were relatively small, typically, at least initially, most of the studies had enrolled patients who had long disease rations, so patients who had the disease onset 10 years or 20 years before, and that was really making it impossible to say whether the changes that were identified were really a cause of MS or whether they were a consequence.

Emmanuelle Waubant, MD (guest speaker):

Because by the time patients have had MS for several decades, they may have changed their diet. They may be on different medications that can affect the gut microbiome, including some of the disease modifying therapies, such as the interferon or the fumaric acids or the anti-CD20 agents, and then making it really very challenging to actually say whether for sure the changes could be causal or not. And so as such I think that there's been several bacteria that appear to be either increased or decrease in abundance in patients with MS compared to controls. But very few studies have really looked very early on, within the first year after disease onset, before patients were on treatment, and then the link to your question is then you can look at the gut microbiome as a disease modifier. So in patients who have an established MS, is the gut microbiome contributing to increase the risk of relapse toward the risk of new MS lesions?

Ruth Adewuya, MD (host):

I think that's such a great way to frame it as opposed to the cause or consequence. My question as you were talking was why is there work being done to understand more about the gut microbiome, but then when you frame it the way you said, does it impact whether it's relapsing, remitting, then that's why this work continues to be important and relevant?

Emmanuelle Waubant, MD (guest speaker):

Yeah. And I think that my strong bias, there's a lot of work that's being done trying to sort out whether the gut microbiome contributes to MS susceptibility, which some of that work I'm actually also doing, but I don't think we'll be able to come up with something very definitive just because of these long, silent phase of MS that precedes that clinical onset. And also if you knew whether there were specific groups of bacteria that were associated was increased risk of developing MS, then you could think maybe more carefully about molecular mechanisms that may be at play. But the truth is that for all the patients who have MS, this would probably not have any benefit for them. So I think understanding whether the gut microbiome can modulate the severity of the disease or the disease activity in my mind is much more important because that brings us closer to developing new treatment strategies.

Ruth Adewuya, MD (host):

That's very well said. Perhaps you could give us a little bit of insight into the different subtypes of MS and how do those microbiome findings compare for those different subtypes?

Emmanuelle Waubant, MD (guest speaker):

Talking about the different subtypes, there's not that much that is known between the different subtypes to recapitulate briefly what is known. I think that the vast majority of the studies have looked at relapsing remitting MS and trying to understand whether specific bacteria are associated with the risk of MS progression is easier to do earlier on in the disease onset process, as we were discussing before. And once you start looking at progressive MS, then you start having even more confirming factors, for example, constipation, which is frequent symptom of progressive MS, can actually alter the microbiome profile. And so that's why we need to really focus first on a type of MS where our findings may be a little more definitive than in patients who have more advanced pieces of MS with increased disability and taking more medications, first because they're older, so age is a big factor in modifying the gut microbiome and then different medications, even vitamins, can change actually that microbiome.

Emmanuelle Waubant, MD (guest speaker):

For patients who have more severe MS, or more advanced disability related to MS, they're more likely going to have repeat urinary tract infection, get antibiotics, have constipation beyond medication for constipation and urinary symptoms. So this medication can add to basically what we find in the stool samples from the patients in terms of some of it has really nothing directly to do with MS. And that's why I think for the relapsing remitting type of MS, I think it's a little easier to know exact time of onset, also, at least a clinical onset. Whereas, for patients who have progressive MS, they've had typically longer disease duration, it's really hard to know for the primary progressive MS patients when the disease clinically started because the onset is very insidious so sometimes we can make a five to 10 year mistake in terms of when they first started to have symptoms.

Emmanuelle Waubant, MD (guest speaker):

So I think that comparing the different types of MS may be scientifically relevant, but in my mind that's not the big push where we should go. I think really understanding if we see more flares or more neural lesions on the MRI, really to some bacteria is probably a low hanging fruit. And something more challenging is to define whether patients who have progressive MS and that would take really longitudinal studies for many years to capture samples from patients with progressive MS and try to see whether there's any specific bacteria or clusters or bacteria that may explain the progression of disability.

Ruth Adewuya, MD (host):

What about the link between the microbiome and inflammation?

Emmanuelle Waubant, MD (guest speaker):

We know that the gut microbiome has a very strong influence on the immune response, and it can happen either through the presentation of small micro portions to the immune cells, to train them in terms of how they develop their ability to have a memory to respond to different antigens. But the microbiome can also modulate the immune response by the metabolites that are generating by bacteria that digest foods. So the different bacteria are meant to break down foods in smaller portions, that then some of it can be seen in the lumen of the sign and be presented to immune cells. And then these immune cells in turn develop [inaudible 00:18:06] in training, so we see new things and they react one way or the other, they can develop a pro-inflammatory response or an anti-inflammatory response so we know that some metabolite can actually have some kind of protection, offer some downplay of the inflammation, whereas some others actually will promote inflammation and then the modulation can occur at the local level, so within the guts and the lining of the gut, but also at the systemic level.

Emmanuelle Waubant, MD (guest speaker):

So some of these metabolites are actually released in the bloodstream and some of these metabolites can actually even trigger some receptors within the central nervous system, and they can stimulate or inhibit some important receptors for the immune response in the central nervous system. But in addition, you can think also of several types of bacteria promoting leakiness of the gut, which means the metabolites can pass in the systemic blood even more easily. So lots of different ways, there are links between the microbiome and the inflammation.

Ruth Adewuya, MD (host):

I know that we've been talking about bacteria, do you agree that this focus on microbiome analysis seems to be on bacteria? Should we be focusing on fungi, for example, or viruses? And do you think that those will be significant in this conversation as well?

Emmanuelle Waubant, MD (guest speaker):

Absolutely. I think that even when you're studying the bacteria, there's actually is the tools that have progressed over time, there are still some bacteria that are identified for which we know that samples can include genetic material from bacteria, but the bacteria, some of them, they don't even have a name. So there's actually many that are found in samples that don't have a name so we don't know exactly what they do, just because in the world of microbiology there's many new agents that actually have still to be discovered in terms of understanding their characteristics basically. And I think it's even more true in the virome world. So there are tools now that have become available to look at the virome and the fungome, and people have started to look at that, but there's general knowledge about the

virome and the fungome, for example, in the gut, which makes it difficult because even if you can do sequencing, you have a difficult time to linking really your findings to the precise agents that have been identified. So I think it's important because also the viruses and the fungi can influence the bacterial communities.

Ruth Adewuya, MD (host):

Just hearing you talk, it sounds like there's a lot that we don't know about causality and consequence, there's some renewed focus on specific areas that hopefully will result in therapies that help patients. How might you predict the most effective ways of manipulating the gut microbiome? I know there's conversations and research done around antibiotics, probiotics, diet, or fecal microbiota transplantation.

Emmanuelle Waubant, MD (guest speaker):

I think that's a one million question at least, but it's fascinating. And I think what we really need to understand are the limitations of different strategies. So right now I would expect that microbiota transplant is probably not a viable option to treat patients. And for many reasons, I think that most of the microbiota transplants that have been done, so right now there's a few small studies of gut microbiota transplants in patients either through colonoscopy or administration in pellets that were released only in the gut, not destroyed by the acid in the stomach. And these options is typically the studies are actually doing one administration and we know from animal, but also other studies that have been done in other disease in humans, that you probably need to have delivery that is lasting several weeks, maybe even several months before you can manipulate the microbiome in a sustainable manner.

Emmanuelle Waubant, MD (guest speaker):

The transplant is also complicating because of the way you can do it, but also the characteristics of the samples. Would you get samples from healthy individuals? But that can be a fair amount of variability from one batch to the next, because two samples may come from the same individual and then the three next samples are coming from three different individuals and they may have different microbiome, and so is it really what we want to do, and then it becomes really expensive. So I think other manipulation options, some people have looked mostly in the animal model at antibiotics, but I think antibiotics on the long term could have negative impact on bacterial communities and possibly selecting resistant pathogens. So that's also something that if you could treat someone for a few weeks and then the microbiome would remain altered in a way you want it to be altered, then that's feasible.

Emmanuelle Waubant, MD (guest speaker):

The tendency is that your microbiome is going to reverse to previous, unless you change, for example, your diet, your exercise pattern, some of your ongoing medications. So that's why I think that other ways to manipulate the gut microbiome are maybe more promising. I think that I have more hope in the probiotics, for example, or the live biotherapeutics or diet, because this could be administered over a long period enough that they could induce and maintain changes as opposed to just treat for a few days and then hope that things are going to stick. From a manufacturing standpoint, it may be also easier to use probiotics or live biotherapeutics than healthy donor microbiota and would have a more reproducible characteristics and human samples. That being said, I'm not saying everybody should be on probiotics because the truth is that there's thousands of different probiotics. So really what we need to do, we need to understand what are the different bacteria that may be critical in modulation of MS

activity, whether it's relapses or new lesions on the MRI or progression of disability, because then you would pick the right mix of bacteria in a given probiotics.

Ruth Adewuya, MD (host):

You answered my follow up question, it's important to choose the right ones, because I think about the clinicians who are treating MS patients. What would your takeaway for them be around thinking about the gut microbiome? What kind of clinical advice should they be giving to their MS patients? And I understand that I'm speaking broadly, because no one patient is the same. What would your advice be for other clinicians who are wrestling with some of these questions that their patients might be bringing to them actually?

Emmanuelle Waubant, MD (guest speaker):

I'm working on some microbiome projects, but I'm also working on some diet projects and trying to combine these two aspects because then we start having a bigger understanding of the situation. I think that at this point I don't advise my patients to go on specific probiotics, so some of them may have to go on probiotics because they have recurrent urinary tract infections and urologists are starting to use probiotics as a way to actually decrease the risk of urinary tract infections. But other than that, I don't have any strong argument to say that all the patients with MS should be on probiotics because we just don't know.

Emmanuelle Waubant, MD (guest speaker):

In terms of diet, I think the situation more challenging, but taking from what is recommended to be a healthy diet, some people would refer to the Mediterranean diet or diets that include lots of fruits and vegetables, not too much saturated fats, for example. These are diets that are healthy for humans in general, for cardiovascular health, for a risk of stroke and so on. And I think this is the only thing I can say at this point for patients with MS, is try to have a diet that is recommended by the college of cardiologists for good cardiovascular diet, because we know that this diet cannot hurt. Now, whether it helps prevent MS flares, MS progression, this needs to be determined.

Ruth Adewuya, MD (host):

I'm just curious, can you talk about the work that you're doing around nutrition and diet and that intersectionality with others? Can you share anything about your work right now?

Emmanuelle Waubant, MD (guest speaker):

Yeah. One thing I didn't mention, when one studies gut microbiome is that it's really ideal to include the study of diet in those patients from whose samples are taken, because there's actually a lot of variability and that's been one of the issues during microbiome studies, for example, in the country as big as the US, is the diets are actually very different from one location to the other. If you take someone from the Midwest and somebody from LA or somebody from Boston, they're going to have a very different microbiome just because of where they live and the type of access to food they have and culturally the type of things people like to eat.

Emmanuelle Waubant, MD (guest speaker):

So what I can say is that in the past we have reported that in pediatric MS onset, higher saturated fat intake seem to be associated with the worse risk of relapse. And the reverse was seen for consumption

of vegetables, the higher the diet was in vegetables, the lower the risk of relapse. And that's some work we're trying to reproduce with a new sample of patients, but as you can hear is basically what's interesting is that it's going back to the notion of a healthy cardiovascular diet.

Ruth Adewuya, MD (host):

That is exactly what I'm hearing. It sounds like it's not that there is, at least right now, not a unique diet for MS patients, but if everyone tried to eat a healthy diet, it's not going to hurt. Any last insights on this topic that you'd like to share with our audience as we wrap up our conversation?

Emmanuelle Waubant, MD (guest speaker):

My take home message is that at this point we need to really narrow down the kind of bacteria that are important in terms of modulating the course of MS before launching in proof of concept trials, because the proof of concept trials are very extensive to employment correctly and so we would need several hundreds of patients to actually enroll in this kind of trial and monitor them for at least six months or a year, and if we don't have the right intervention, so if we pick the wrong bacteria, we take blindly one probiotic among thousands of probiotics, then it could be a waste of time and resources. So I think it's really important to go step by step, not jump through any of these steps that are very important to try to design the best study so we have the higher chance of answering the question, whether yes, an intervention that modulates a microbiome has the potential to modulate disease activity or disease causing MS.

Ruth Adewuya, MD (host):

Thank you so much for chatting with me today and for sharing your insights on this incredible topic. I look forward to hopefully coming back and chatting with you about your work as some more innovations are made in this space. Thank you for your time today.

Emmanuelle Waubant, MD (guest speaker):

Thank you for inviting me.

Ruth Adewuya, MD (host):

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