Akiko Iwasaki, PhD, on the latest long COVID-19 research [Podcast]
Unger: Hello, this is the American Medical Association's COVID-19 Update. Today we’re talking with Dr. Akiko Iwasaki, the Sterling professor of immunobiology at Yale University and a principal investigator at the Howard Hughes Medical Institute, who’s going to share with us the latest research on long COVID. I’m Todd Unger, AMA’s chief experience officer in Chicago. Dr. Iwasaki, thanks so much for joining us. We hear and read a lot about long COVID. It sounds scary and concerning. And the more complicated diagnosing and treatment that seems to accompany it these days. Why don’t we just start by talking about, at this point where we are with the pandemic, is there an agreed upon clinical definition for long COVID? Tell us a little bit about the symptoms and how you classify it now.

Iwasaki: Right, so there is no universal clinical case definition for long COVID but the CDC definition says that new and returning or ongoing health problems in people who have at least four or more weeks after the first infection with SARS-CoV-2. The WHO definition is similar but they usually say within three months of initial diagnosis and symptoms lasting for over two months. And so slight difference but overall, at least four weeks if not two months or 12 weeks is used by another agency.
The types of symptoms that are reported is vast. There are over 200 symptoms being reported for long COVID. That includes things like fatigue, shortness of breath, memory impediments and GI symptoms, many, many different organ systems being involved.

**Unger:** What do you think of those symptoms are the most predominant ones? I heard you say, I guess, the colloquial term of brain fog is something we've heard about before but in terms of severity and incidents, are those the top ones on the list?

**Iwasaki:** Yeah. If you look at all the different surveys, fatigue is the number one symptom that's being reported, followed by cough, headache, muscle pain. Loss of taste and smell is also one of the top symptoms, as well as sore throat, shortness of breath. But as I mentioned, there are over 200 symptoms.

**Unger:** I mean, when a patient presents themselves with some set of symptoms coming after about a bout of COVID, how is a physician to work with that when there are 200 in contention?

**Iwasaki:** Right, so that's the other issue is that we really need a guidance for the physicians to be able to diagnose properly long COVID because not every patient has obviously all these symptoms. They may have one or two and some people have more than a dozen symptoms. So we really need to educate the physicians to be able to diagnose long COVID properly.

**Unger:** Back when we were earlier in the pandemic, I spoke with someone that talked about how they were trying to quantify how many people or what percentage of people were developing long COVID symptoms. I think at that time it was much higher than we anticipated, somewhere in the 20 to 30% range. What are we seeing now that we're past two years in the pandemic?

**Iwasaki:** Yeah. So there are many reports that define the prevalence of long COVID in survivors of COVID. And we can think of this in two bins. One is patients who had severe COVID, who were hospitalized and are discharged alive from the hospital. And in that population, the percentage is up to 50%, whereas people who had mild or even asymptomatic infections, they can develop long COVID over time within about three months of that infection. And that tends to be between five to 30%. They vary because we don't have a universal definition of long COVID.

**Unger:** Those are high numbers, so that's a really interesting thing. We're going to talk about that in regard to what challenges for the future. But one thing I'm curious about, you read a lot about, a lot of folks are trying to figure out why this is happening. What is the current thinking and what does your research support in terms of one theory or another, if that is even where we are?

**Iwasaki:** Yeah. So currently we are at the hypothesis stage. We don't have a concrete answer as to what's causing long COVID but there are a few things that I can name. One of the top hypotheses is the persistent virus or viral remnants that are persisting in tissues, such as viral RNA or protein or...
both, and that could be triggering chronic inflammation in these people. The other hypothesis is autoimmunity. So an acute respiratory infection can induce autoimmune conditions in some patients. Once that’s developed, it's very difficult to reverse that process. And that could be happening in a subset of long COVID patients. There’s also hypothesis about gut microbiome that's dysregulated, dysbiosis, as well as latent virus reactivation like EBV. So there are many of these hypotheses and I believe long COVID is likely composed of multiple diseases that are under one umbrella but needs to be really disassociated and disentangled.

**Unger:** Those are a lot of hypotheses to explore. I guess, it sounds as you’re talking about it, we’ve been learning in real time with the pandemic itself. And I guess we’re in the same situation with long COVID at this point. So the question as to why is it so challenging to figure out and what kind of research and how to gather data, I’m hearing from you, we’re early in this still. Is that how you would classify that?

**Iwasaki:** Yes, I think so. It's not for lack of trying. We are working very hard to try to understand this disease. Because we don't understand the cause yet, it is triggered by the infection but downstream what's causing it is still unclear. We are basically monitoring every possible parameters in the patient, so we can understand if there may be a persistent virus or RNA, or a latent virus reactivation or autoimmunity. These assays require distinct assays to be able to show autoantibody versus viral remnants and so on. It takes time, but we are making progress.

**Unger:** Dr. Iwasaki, one thing I'm interested in is scientists have seen physical changes evident in people who have long COVID. What are some of these kind of physical changes? And talk a little bit about the science that might help explain them.

**Iwasaki:** Yeah. So there are definitive changes that people are measuring in the long COVID patients. For instance, the UK Biobank did a study where they measured a COVID survivor's brain mass before and after the infection. The UK Biobank is great because they're monitoring for brain MRI, just sort of continuously in people. They were able to capture people prior to their COVID exposure and post-exposure, and compare that to a control group that's age matched who haven't been infected with COVID. And what they found is that there was a greater reduction in the gray matter thickness than the uninfected matched controls and also greater changes in markers of tissue damage in regions connected to the primary olfactory cortex and also greater reduction in global brain size. So these even happened in non-hospitalized patients and that's a real sort of physical change that we are able to monitor. But it's first of, I believe, many studies that's going to find physical changes in long COVID patients. What can explain these kinds of brain mass reduction? It's unclear but I believe inflammation is involved.

**Unger:** Wow, that is really concerning. And you mentioned before in the arena of say autoimmune disorders, that some of these things, they're just, at this point, not reversible. Is that kind of an overarching theme here?
Iwasaki: Well, I don't want to give off the impression that long COVID is permanent because a fraction of people are recovering gradually. If you follow the course of these symptoms over time, there's a definite gradual reduction but it's not going to zero. So it's really those fraction of people who are still suffering after two years of having had COVID. How do we treat those people? And is there something that we can do to reset or reverse the disease? Again, depending on the disease etiology, the treatment will be quite different.

Unger: We talked a little bit before, just kind of translating this into practical world of a physician who has a patient walk in that could be one of the set of 200 different symptoms but really post-COVID infection. How do you advise a physician in terms of what the first step is in treatment?

Iwasaki: Well, right now we lack enough data to be able to advise the physician as to the treatment options. But what we really need to do is to understand these different endotypes that underlie the disease called long COVID. If there are four distinct endotypes that are caused by different things, we need to treat them differently. So for each endotype, we need a biomarker or biomarkers, and then we can separate the patients into the right kind of disease treatment pathways. So if the patients are suffering from autoimmunity, we need to give them immunosuppressives. And if the patients are having persistent virus infection, we need to give them antivirals. The kinds of treatment would obviously differ depending on the cause of disease.

Unger: You know, with the percent of people that you were talking about and some of these wide range of symptoms, I guess it's not surprising that you've talked previously about a concern about a parallel pandemic of long COVID patients that could be on the horizon. It's kind of a pandemic after the pandemic, I guess you could say. Is our health system equipped to care for these patients and if not, what do we need to do?

Iwasaki: Yes, it is a parallel pandemic because it's happening at the same time as the acute infections are happening. And it will be a much longer lasting pandemic than the acute infections because people are going to be suffering for four months. Our current health care system is not well equipped to care for the millions of people suffering from long COVID. The patients need a coordinated care system, really, where they can be plugged into a network of physicians specializing in long COVID issues, whether it be a cardiologist, neurologist, pulmonologist, gastroenterologist, dermatologist or whatever they need. And they need to be all educated to be able to recognize and treat the patients appropriately. I think there should be a coordinated care that the physicians can see these patients immediately through a network of specialists and that doesn't really exist in many places.

Unger: Last question. You were one of a group of public health experts that issued a 136-page document about moving the nation into what you call the next normal, which outlines strategies for living with COVID-19 in the future. And of course, one of those 12 key focus areas in the report is about long COVID. How do we live with long COVID going forward?
Iwasaki: Yeah, so we did write a roadmap for the next normal and our chapter was on long COVID. I'm delighted to announce that President Biden announced a plan for dealing with long COVID. And many of what we proposed were actually incorporated in that document. So very, very pleased that the administration was keen on incorporating many of the suggestions. Basically what we proposed and are incorporated in this new strategy is establishing a task force that coordinate interagency activities because there are many agencies that are working on long COVID but the coordination is lacking so far. And we also need to create scientific and regulatory response for characterizing and then counting really long COVID and also understanding the basic disease pathogenesis so we can start doing planning for clinical trials based on that understanding. Again, as I mentioned, there needs to be a consensus-based guideline for these interdisciplinary care models for clinical treatment and management of long COVID. And of course, we need to ensure adequate health and social support is provided to the patients.

Unger: Dr. Iwasaki, thank you so much for spending time with us talking about this. It's clearly just a critical area for us to understand. I want to thank you also, and you and your colleagues, for all the work that you're doing to try to bring some light to what is a very, very dark problem right now. That's it for today's COVID-19 Update. We'll be back with another segment shortly. In the meantime, visit ama-assn.org/COVID-19 for more resources. Thanks for joining us today. Please take care.

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