New clues to the biology of long COVID are starting to emerge

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NOEL KING, HOST: Scientists are starting to understand what's happening with long COVID, the condition where people suffer with health problems months after getting sick with COVID-19. NPR health correspondent Rob Stein has the latest information.

ROB STEIN, BYLINE: Kelly LaDue thought she was done with COVID-19 after a miserable couple of weeks being tormented by the virus. She even went back to work, thinking the worst was over.

KELLY LADUE: And then I started with really bad heart racing with any exertion. It was weird.

STEIN: Because she didn't have that when she first got sick.

LADUE: Walking up the stairs, I'd have to sit down and rest. And I was short of breath brushing my teeth. I was a - everything - I had to rest after everything I did.

STEIN: A year later, LaDue, who's 54 and lives in upstate New York, is still a wreck - bad headaches more days than not, sudden high-pitched whistling in her ears, bizarre phantom smells and vibrations in her legs, aches and pains all over her body, brain fog so bad she had to quit her job as a nurse and is afraid to drive.

LADUE: These symptoms, they come and go, and you think it's gone. You think this is it. I'm getting better. And then it'll just rear back up again.

STEIN: Patients like LaDue have researchers scrambling to figure out what's going on. Estimates are all over the place about how often COVID-19 leads to long COVID. But even if a small fraction of the people who've had COVID are left struggling long term, it's a major public health problem that could go on for years.

ANGELA CHEUNG: I think it's the post-pandemic pandemic.

STEIN: Dr. Angela Cheung is studying long COVID at the University of Toronto.

CHEUNG: If we are conservative and think that only 10% of patients who develop COVID-19 would get long COVID, that's a huge number.

STEIN: So far, there are more theories than clear answers for what's causing long COVID. Maybe the virus is still hiding in the body somewhere directly damaging nerves in other parts of the body. Or maybe the virus isn't still directly causing problems but keeps the immune system kind of simmering at a low boil, causing the symptoms. Maybe the virus is gone but left the immune system out of whack and is now attacking the body instead of the virus. Akiko Iwasaki, a professor of immunobiology at Yale, is trying to sort it all out.

AKIKO IWASAKI: It's still early days, but we believe that long COVID is not caused by one thing, that there are multiple diseases that are happening.

STEIN: Iwasaki and others have started finding clues to what might be going on, like proteins produced by the immune system known as autoantibodies, which may be attacking cells and tissues in the body instead of the virus. They also found unusual activity by cytokines, chemical messengers the immune system uses to communicate.

IWASAKI: We are finding elevated cytokines in long COVID patients, and, you know, we're trying to decode what those cytokines mean.

STEIN: Other researchers have produced similar findings. Dr. Steven Deeks at the University of California, San Francisco, found some long COVID patients appear to be left with elevated levels of a cytokine called interleukin-6, suggesting they may be suffering from a state of chronic inflammation.

STEVEN DEEKS: The first couple weeks of the infection is associated with a, you know, massive amount of inflammation, and the virus just blows up the immune system. And so it's reasonable to think that in some people, the acute COVID results in an inflammatory state which can contribute to long COVID over time.

STEIN: Though even people with mild cases can end up with long COVID. Other researchers have detected a different clue in the immune system - an unusual pattern of activity by immune cells called T-cells that may support the idea the virus is hiding in their bodies. Dr. Igor Koralnik is at Northwestern.

IGOR KORALNIK: That's a signature or pattern which could be consistent with a low-level but persistent infection in the long COVID syndrome patient.

STEIN: But others are not so sure any of the evidence produced so far is very convincing, including any signs the immune system is the problem - a so-called autoimmune disease. Dr. Michael Sneller has been studying hundreds of long COVID patients at the National Institutes of Health.

MICHAEL SNELLER: So the thing that has struck me most now in a year and a half of seeing these patients and extensively testing them is that we are finding little to no abnormalities.

STEIN: He's tried every test he can think of.

SNELLER: Echocardiogram, pulmonary function tests, X-rays, brain MRIs, you name it, laboratory markers of organ dysfunction - not seeing any of that - and precious little evidence of immune activation looking just at the sort of the standard markers of inflammation. I'm running out of tests to do, basically.

STEIN: But Sneller hasn't ruled out anything and is still looking, including doing more detailed studies of the immune system, as well as psychological testing, because he agrees people are suffering real, long-lasting problems.

SNELLER: It's 100% real. These people have these symptoms - absolutely. The question is what's causing them. You know, just because you can't find - I mean, anxiety produces real symptoms. The symptoms are real. It's just they're not due to any damage we can pinpoint.

STEIN: But Akiko Iwasaki at Yale is convinced the immune system is playing a key role.

IWASAKI: There is definitely something going on there. We need to know what that is. You know, we need to understand what's going on in each patient because the treatment option will be very different depending on what they actually have.

STEIN: Perhaps antiviral drugs could eradicate any virus still hiding in the body. Perhaps the vaccines could do that, too. Some patients have gotten better after being vaccinated. Or perhaps drugs that dampen down the immune system might help. Kelly LaDue just hopes researchers eventually figure out what's going on with her and other patients.

LADUE: I want to feel normal. And I hope to be back to normal again someday and not ever even have to think about it or worry about if I can do something. And the hardest part definitely is trying to look and be normal but not feeling normal.

STEIN: Rob Stein, NPR News.

(SOUNDBITE OF MADRID'S "JUNE PARK")