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NIH Study Identifies Cause for Long COVID Neurological Symptoms

Dr. Turck:
A group of researchers at the National Institutes of Health studied 12 people who had long-lasting anddisabling neurological symptoms after they had COVID-19 infection. The trial showed these patients had differences in their immune cell profiles and autonomic failure. So what can we learn from this new research to help us diagnose and treat patients with long-term COVID-19 symptoms?

Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and joining me today to discuss the findings of this study is Dr. Avindra Nath. Dr. Nath is the Clinical Director of the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland.

Dr. Nath, welcome to the program.

Dr. Nath:
Oh, thank you, Dr. Turck, for having me on the program. It's a real pleasure.

Dr. Turck:
Well, before we dive into the study, Dr. Nath, would you tell us what symptoms are consistent with long-term COVID-19 infection?

Dr. Nath:
Yeah. So I think one of the problems with the term Long COVID is that nobody really knows exactly what it means. So you have patients who have acute symptoms with COVID, they get better from it, and then symptoms continue or new symptoms develop; and the patients started saying, "Well, I have Long COVID," so it really is a term put together by patients. There are other terms that other organizations have tried to come up with. The WHO has a definition where they call it Post COVID, and we have NIH that calls it PASC, Postacute Sequelae of COVID. Well, they are all very complicated terms, and they really don't tell you much, but Long COVID could very well be a number of syndromes under one umbrella with multiple different pathophysiological mechanisms, but what is important is that you have a subset of individuals who were admitted in the hospital, came out, and then they have persistent symptoms. That could very well be explained by what they got through multiorgan involvement during the acute phase. That should not be mixed up with the other set of patients, which I like to call Long COVID, which is those individuals who never went to the hospital, had very mild symptoms, stayed at home, and then when they recovered from it, they started getting after a few days or weeks some new symptoms that arise. And these symptoms can be exhaustion, exercise intolerance, mood instability, cognitive difficulties. They can have pain syndromes or dysautonomia. So those in my mind have a very different underlying pathophysiological mechanism, and that really is what most people really mean by Long COVID.

Dr. Turck:
Now you mentioned the pathophysiologic mechanisms. Before this study was conducted, what did we know about the pathophysiology behind long-term COVID-19 symptoms?

Dr. Nath:

The problem is there's a lot of studies out there trying to understand underlying pathophysiology or underlying immune abnormalities and the like. Most of them have been done either in the acute or the subacute phase. And because the pandemic is relatively new, capturing patients later in the phase is not that easy, and so yes, we have some idea of what's really happening in these patients. We have autopsy studies in acute phase that is some of which we did ourselves. We have people looking at blood and cerebrospinal fluid for these kind of abnormalities, but what is unique about our study is that we characterized a subset of individuals that truly had neurological manifestations that could be attributed to COVID that originally had mild symptoms but not to the severe form of acute symptoms, but rather, truly, there were symptoms that arose after having recovered from the acute symptoms and were truly neurological in nature.

Dr. Turck:
Now turning our attention to your study, Dr. Nath, how was it designed?

Dr. Nath:
So we screened over 170 individuals who were complaining of various kinds of symptoms, having recovered from the acute phase of COVID. From there we distilled them down after reviewing their medical records, talking to them to make sure there's no other underlying condition that could account for their symptoms, and then finally enrolled 12 people that were quite pristine, and one could be absolutely certain that, yes, that is something that happened in the context of COVID, but this is what you would call Long COVID and cannot be explained by any other underlying disease.

Dr. Turck:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Avindra Nath about the pathophysiology and symptoms of long-term COVID-19 and talking about the design of a study that recently examined them.

Now that we've covered how the study was designed, Dr. Nath, what were the findings of the study?

Dr. Nath:
Yeah. So a hundred percent of these individuals had fatigue, and they had cognitive difficulties. And then a variable number of individuals then either had palpitations or they were complaining of tingling-like sensation, which we call paresthesias; some had loss of smell and taste that persisted; some had dizziness; some had psychiatric symptoms; some had tremor; and some even had small number of them even had seizures.

Dr. Turck:
And you had some findings that were suggestive of autonomic failure?

Dr. Nath:
So all of these patients underwent very detailed MRI scanning of the brain. We did spinal fluid evaluation on them, looking for various kinds of new markers and lots of other potential biomarkers in the spinal fluid, and they had detailed immunology done in the blood. And we also did a lot of autonomic testing, as well as looking at the peripheral nerves or the possibility of neuropathies and the like.

What we found was that interestingly this small subset of individuals had a lot of immune abnormalities and one of the most striking observations was that almost all of them had B-cell activation, so they had these B-cells that we call antibody-secreting B-cells. They were increased in each of the individuals compared to healthy controls. Then they had some abnormalities in other cell types as well. So for example, the T-cells themselves were actually decreased. Those are cells that are important in very precise attack against the virus so suggesting that those cells were actually decreased while the antibody-secreting cells were actually increased. And we also found what is called a checkpoint. So these are immune exhaustion markers, and they were increased in T-cells, as well as in monocytes, so suggesting that there's something wrong with the T-cells where they're unable to do their job, they're exhausted. But instead, what we are getting is the innate immune response, which is the NK cells and the B cells that are activated. So I think that itself is telling you something very important about how the immune system is really dysregulated in these individuals.

We also looked at their neurotransmitters because we wanted to see if there were any abnormalities to explain the dizziness and the palpitations that they were experiencing, and sometimes the cognitive dysfunction may also be related to changes in these systems. So what we found was that in these patients there are some metabolites of dopamine that were actually increased in these individuals, as well as metabolites of norepinephrine, which is another neurotransmitter, and so that suggests to us that there is some abnormality occurring in the catecholamine pathway as well. And that correlates well with when we looked at their autonomic dysfunction because we found that their heart rates were actually lower resting heart rates in these patients compared to healthy controls, and there were signs of other autonomic dysfunction as well, so that could explain these symptoms of dysautonomia that these patients were having.

Dr. Turck:
And how could your study's results field further research?

Dr. Nath:
Yeah. So they are very important. So number one, it tells you that you have to properly characterize your patients, and you can clearly show that these patients have a true underlying biological basis for their symptoms, so both of the immune system and neurological function. And so future studies should be done in larger sample sizes to confirm these observations, but it also provides you an opportunity for intervention. So one of the things that I feel quite strongly about is that it's important to understand the pathophysiology, but you can do that in the context of clinical trial because we have a lot of people who are suffering from this disease. It's true that we may not understand all the pathophysiology completely, but I think we know enough to be able to start thinking about ways of intervention and yet in that process, try to characterize the pathophysiology even further.

Dr. Turck:
Dr. Nath, as we come to the end of today's program, are there any additional thoughts you'd like to leave with our audience today?

Dr. Nath:
So what I would say is that patients who are suffering from symptoms of Long COVID should seek help from specialized clinics, and physicians that are now getting quite a lot of expertise in treating these patients. Sometimes it takes a multidisciplinary approach, but there's a lot that can be done for them right now even if it is symptomatically. And then I'd urge the physicians and the researchers to try and think about designing clinical trials using immunomodulatory drugs and the like so that we can quickly determine what can make a long-lasting effect to the lives of these patients.

Dr. Turck:
Well, this has been such an insightful look at new data on the neurological symptoms of patients with long-term COVID-19, and I'd like to thank my guest, Dr. Avindra Nath, for joining me today and sharing these new findings.

Dr. Nath, it was a pleasure speaking with you today.

Dr. Nath:
Likewise, Dr. Turck. Thanks for having me on your show.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit ReachMD.com/NeuroFrontiers where you can Be Part of the Knowledge. Thanks for listening.