

Dr. Avindra Nath

Behind the Mask

January 12, 2021

Gabrielle Barr: Good afternoon today is January 12, 2021 and I have the pleasure of speaking with Dr. Avindra Nath. Dr Nath is the Clinical Director of the Translational Neuroscience Center and the Chief of the Section of Infections of the Nervous System at NINDS (National Institute of Neurological Disorders and Stroke). Thank you very much for speaking today about some of the COVID-19 programs you are helping out with as well as your own COVID-19 research.

Nath: Thank you very much for having me on this show here. I am absolutely delighted to be able to participate in this process and to share our experience and our projects with you.

Barr: That's great. To get started, what types of neurological issues can patients who contact COVID-19 experience? Then I would want to follow up with why, exactly; it seems like a mystery.

Nath: One can largely divide the types of complications into two categories. The first occurs during the acute phase of the illness, and the other is what we call, "post-viral syndromes". During the acute phase of the illness, patients can develop loss of smell. They can become confused; sometimes become delirious and have hallucinations. We call that an encephalopathy. Some patients can develop strokes. Others can develop seizures.

Now after the patients recover from the acute phase of the illness, a number of immune-mediated syndromes can occur. Some patients can develop a massive inflammation in the brain and spinal cord. It's called acute disseminated encephalomyelitis. That's the term often used to describe them. Sometimes they can get bleedings in the brain manifesting as small hemorrhages within the brain.

Then there are a whole host of patients who complain of symptoms that have been termed long-COVID-19 or long-haul COVID-19. These patients complain of brain fog. They may complain of getting dizzy every time they stand up, or their heart races, or they have chest pain, or low-grade fever that persists. There are a wide variety of symptoms that can occur in this patient population.

Barr: I have a question of why? I have read that in a lot of these patients, their brain isn't directly being infected by COVID-19. What exactly is causing these symptoms? Is it nerves being infected in other parts of the body or just an immune response? Can you shed more light on that?

Nath: Yes, you are absolutely right. The virus infects the nasal passages and can infect the lungs and the respiratory passages. It is going to the lungs. However, when we looked at the brain, we didn't find any virus, although we found a lot of pathology there. It turns out that the virus doesn't circulate in the blood very much. If virus is found in the brain, it's present in a very, very small amounts. That cannot really explain the symptoms that these patients have. We think that a lot of the pathology is due to inflammation and that's probably driving damage to the blood vessels and subsequently within the brain causing pathology as well.

Barr: Have you noticed any patterns in neurological symptoms amongst patients, like those in certain age brackets getting one particular type of symptom or those in certain genders getting others, or something like that?

Nath: Yes, at the extremes of age you see a slightly different pattern. If you look at older individuals, they are at more risk of developing brain pathology and dementia-like syndrome, loss of cognitive function. The brains are already compromised and if you have another injury on top of it, they can't really handle it. And the young population, the children, they are getting this massive inflammatory syndrome, which is called multi-system inflammatory syndrome. A lot of organs get involved due to the inflammation.

Then with regards to gender in the acute setting, there is not that much of a difference. But in the chronic setting you get this long-haul COVID-19 or long-COVID-19. It turns out that it's more in women compared to men; some studies show four times more in women compared to men.

Barr: Wow, that's a lot. Do the brains of those experiencing a range of symptoms look different than those that may just have one or two symptoms?

Nath: That we do not know. The thing is that we don't have autopsy tissues from patients who have had long-haul COVID-19. I think that is what you are referring to, one to two symptoms or a lot of symptoms and how that may correlate with etiology. We don't really know. But what one would like to do, is to get MRI scans of the brains. We may be able to figure it out that way and also look at their spinal fluid. Those studies are now underway. We don't have the answers quite yet, but our hope is that we'll be able to figure it out that way.

Barr: What roles do comorbidities play in neurological issues manifesting in COVID-19 patients?

Nath: It was shown quite early in the epidemic that if you have preexisting hypertension, cardiac disease, or renal disease, you are at greater risk of developing complications from COVID-19 infection.

Barr: Can you speak a little bit about the examination of brain tissue samples from the 19 patients who died of COVID-19 between March and July of 2020? Talk a little bit about some of the machinery that was used to analyze these samples.

Nath: Let me first state, that this is a very unique population because 11 out of the 19, were individuals who died suddenly. They didn't even realize there was anything wrong with them. They may have had some respiratory symptoms but not enough to warrant any kind of medical attention. Yet they were found dead in bed, one died on the subway; one person was just lifting his sister. He was about 30 some years old and just collapsed and died.

Barr: Oh my.

Nath: When we looked at their brains, all of these patients actually had pathology in the brain. It's a very unique population in that way. Remind me again what was the question you asked?

Barr: Can you talk a little bit about how and what was used to analyze their brain?

Nath: What we did was—the brain is huge in size, so the thing is now if you start looking at it under a microscope, you could spend years on a single brain looking for small amounts of pathology. We took parts of the brain and put it in an MRI scanner.

This was the autopsy tissue that was already fixed in formalin. We put it in an MRI scanner and we found was that there were these small dot-like places in the brain that looked abnormal. Then we made sections from those areas where we could see these dots; then we looked under the microscope. That would not have been possible if we had not had the opportunity to scan the brains with these high-field MRI scanners.

Barr: How long did it take to do the analysis?

Nath: It wasn't that easy, even with the scans. The brain scan can take several hours, sometimes days because you are making very fine sections through the whole thing. So, the scanner has to run a long, long time for single tissue blocks. Then we had to make sections and stain them by hand. I had a postdoc, Myoung-Hwa Lee who did all the immunostaining. She worked day and night to do them, weekdays and weekends. We stained hundreds of sections and then analyzed them and then tried to make sense of it. We had several neuropathologists who looked at them. Via Zoom we would share all the images. We then interpreted them together to make sure we all agree on what we are finding in the brain. It was a huge team effort to make this possible.

Barr: Based on the results of that study, have further studies begun on how COVID-19 harms the brain's blood vessels?

Nath: Yes, and that is a very important question that needs to be addressed. Why does the inflammation attack the blood vessel? One possibility is maybe the linings of the blood vessels were infected with the virus and that's why the immune system is going after the blood vessel. Or it's not infected, but some of the viral proteins may be sticking to the blood vessels. You never know and maybe that's how the blood vessels are being compromised. That needs to be studied further. It's not entirely clear, but I think that is a very important question.

Barr: In the situation of the long-haulers; it's very interesting. Have neurologists ever seen a situation like this before with other viruses causing such long-term effects?

Nath: Yes, we have seen it with a number of other viruses; influenza, for example. You know people will recover from it and then they can develop similar symptoms. With Ebola we also saw that occurring and we have seen it with the first SARS virus as well. There were patients who developed long-term symptoms similar to long-COVID-19; Epstein-Barr virus acutely causes infectious mononucleosis. There have been lots of patients with this infected reported to develop chronic symptoms. Yes, it's not that uncommon. Now, whether the long-term symptoms with COVID-19 are different from those we see with other viruses is not entirely clear because here we do have some identifiable pathological effects on the brain. And with the other viruses, it's not entirely clear if it's directly affecting the brain or not. Over time it will become more evident.

Barr: COVID-19's long-term effects to date—there's a lot more research that needs to be done. Some seem more severe than other coronaviruses' effects on the brain and neurological system.

Nath: I think that may be true. The population size affected with the other coronaviruses was much smaller, so we don't really know. But yes, COVID-19 seems to be very lethal and its effects are very dramatic on multiple organ systems including the brain.

Barr: Can we talk a little bit now about some of the NINDS protocols that are evaluating patients with neurological issues that are occurring right now?

Nath: There are two protocols in NINDS (National Institute of Neurological Disorders and Stroke); one is to look at all types of neurological complications that occur in the COVID-19 patients. Anybody with a neurological problem can be brought to NIH and we can study them.

The second is a protocol where we want to bring in people who look very much like what we call ME/CFS; that's myalgic encephalomyelitis/chronic fatigue syndrome. We want to compare it to the garden variety syndrome to study the similarity or differences between the two populations.

Barr: What phase are you in right now with those projects?

Nath: Well, these were recently approved so we're trying to bring in patients currently. There is a restriction on how many patients you can bring into NIH. Recruitment is slow, slower than what we would like to see. But it's still moving along.

Barr: Back to the long-haulers, what do you suggest for their long-term care to be; long-term care with their symptoms? It seems so many of them have almost a permanent problem.

You know they can't smell or taste.

Nath: I think the fact is that there's so much inflammation that is being reported now by a lot of different researchers. One possibility is to do a clinical trial with some anti-inflammatory agent such as corticosteroids, or what have you, to try and see if it makes a difference or not. I think that could be one thing that can be done. One of the questions, I am eager to address is whether there may be restricted or persistent viral activation in the long-COVID-19 patients that maybe driving the inflammation. If present, once could develop targeted curative therapies. But irrespective of that, I think symptomatic treatment should be provided to everybody. There's a lot that can be done symptomatically to treat these infections. You can't cure damaged nerves that are already gone, but at least you can provide some comfort.

Barr: What has been your role in laying the groundwork for and performing some of the COVID-19 research going on in your Institute right now? You talked a little bit about it earlier.

Nath: I'm in the Intramural Program and because my interest is in neurological manifestations of infections, I got involved very early. I hope people will view me as being a strong voice in the community. We really need to look at the neurological manifestations closely and not ignore them. I initiated a number of projects here within our own Institute intramurally. Besides the clinical and pathological studies I described earlier, we are also developing antisense oligonucleotides against the viral genome and a potential anti-viral treatment. I have also been talking to a lot of people to initiate research elsewhere and in other universities as well as to look at this. Our extramural folks have been very committed to try and help, from Walter Koroshetz and several others in our Institution. They are all working together and wherever I can help, I'm happy to do so.

Barr: You're very involved with COVID-19 research. But do you do anything else at NIH that's COVID-19 related, help with any task forces things?

Nath: I'm on the COVID-19 Task Force as well. That's part of my role with NCATS (National Center for Advancing Translational Sciences). They're taking a leadership role in it and I'm on their Task Force.

Barr: It seems like the answer would be both, but have you been working on campus, at home, or a combination. What has your experience been?

Nath: I'm working largely from home, although I do go in from time to time when it is necessary. It has actually worked out well to tell you the truth. I can, because the patient load is less, my need to go in has been much less. The lab that I work in has been functioning well without my physical presence. I meet with everybody on Zoom. In fact, I like meeting via Zoom rather than in person because you're not wearing all these masks. It's very hard to get a conversation going with the mask on. You have to be far apart from one another, and your conversations are short and brief. But on Zoom you can get a much better conversation going. In fact, certain things have worked better, and the commute time has gone down. You know getting meetings put together with multiple people or panels is much easier. You don't have to run around the building to get from one place to another. Actually, there are other advantages. The kitchen is close. I can get up and get something.

Barr: Yes, definitely. Has it brought any challenges for you?

Nath: Well, there are of course challenges. As I said, we're still working at 50 percent capacity. And you know we haven't been able to bring in all the patients we want to. Yes, there are certainly challenges. There's no doubt about that. It goes both ways.

Barr: This is a fun question. What is one thing that you do to relax during the pandemic, It has been a very stressful time.

Nath: During the summer I took up some gardening. I hadn't been gardening much previously; been dabbling a little bit in the past, but I took up some serious gardening during the summertime and planted all kinds of stuff, vegetables, flowers, and fruits. It was a lot of fun.

I got out some old benches that I really wanted to work on. Sanded them down, painted them and set up a few things around the yard. It was a lot of fun. Now I've been kind of cold, so I've been looking at some cooking shows, believe it or not, with my wife and we were doing a fair bit of cooking. For a while there we weren't doing much cooking. We just did what was necessary, but now we've actually dabbled into some fancy cooking here.

Barr: What's the favorite thing that you have made so far?

Nath: Oh, favorite thing. I don't know. We've learned a lot of interesting baking and making chicken a variety of different ways, and soups of different types. I mean it's been actually terrific, [cooking] things that we would actually go to a restaurant [to get]. Now I'm getting a little bit pickier about my food. Next time I go to a restaurant, I'm gonna be looking for some fancy stuff.

Barr: Yes definitely. Well, is there anything else you would want to share as an NIH scientist, but also as a person who's living through the pandemic?

Nath: These are unprecedented times. Humans have never faced anything like this on this planet ever. This will go down in history as some of the most remarkable and the most difficult times; both from a health standpoint and due to the political and social unrest. It has shaken the entire fabric of human society. These are times that should not be taken lightly. We need to learn from this and prevent further disasters from taking place. I think that is extremely important.

The role of NIH has been a very critical one. Today we are fighting about not being able to get enough vaccines. The vaccine would not have been possible if it weren't for NIH. The whole Institution was set up by people who had the foresight to set up a National Institutes of Health, and it was the right thing to do at the time, right after the second World War. Those were very difficult times, but good things came out of it, and what they set up as an Institution is paying back rewards in unmeasurable amounts over the years. It's an institution that should be cherished and should be allowed to grow and should be invested in. Because every penny that you put in, you are going to reap millions of dollars from the scientific discoveries made. I think this is a fantastic place to work and I'm grateful to have the

opportunity to lead the clinical program here and to run my own laboratory research. To see patients here is a real privilege.

Barr: Well, thank you very much for your service and I hope that you, your team, and your family continue to stay safe.

Nath: Thank you, it has been a pleasure talking to you. Take care.