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How Does COVID-19 Affect the Mind?

Dr. Wilner:
You're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Andrew Wilner, and joining me to discuss the neurological effects observed in COVID-19 patients is Dr. Ken Tyler, Professor and Chair of the Department of Neurology at the University of Colorado School of Medicine, where he also holds a Professorship of Medicine and Microbiology. Dr. Tyler, welcome to the program.

Dr. Tyler:
It's great being here. Thanks for inviting me.

Dr. Wilner:
So tell us, what are the qualities of the SARS-COVID-2 virus that make it so dangerous and so lethal?

Dr. Tyler:
Well, first of all, I have to go backwards to your introduction there and say one of the fun things about the field I manage: almost none of the things that I've studied, and COVID-19 would be included in that group, were things we learned anything about in medical school. So we had everything from AIDS to West Nile Virus, to COVID and new things keep on emerging, which makes it fun. And to answer to your question, I think the important thing about COVID is how infectious the virus really is and how widespread it is, which in turn is in part a consequence of the fact that it's predominantly a respiratory virus, and we know that as part of its process of infection, it involves multiple organ systems and so, perhaps, it isn't surprising that the central nervous system is involved, as well. Both, likely indirectly as a result of all the systemic effects and the effects on other organs, that this virus produces, but probably also directly and through the medium of hyperinflammatory state, as well.

Dr. Wilner:
Right, so, it seems that the body mounts a response to this virus that includes inflammation and that, in and of itself is dangerous it seems, is that right?

Dr. Tyler:
Yeah, I think we've learned with a number of other, so-called neurotropic, meaning involving the nervous system, viruses that the immune system can sort of be a two-edged sword that obviously the immune system and different components of it are important for things like the clearance of viral infections. But at the same time, they can also contribute to the injury. And I think we see that in certain circumstances, of course with COVID, where some of the syndromes are probably the result of a kind of post- or para-virus or para-infectious inflammatory response. And that's certainly, probably true for some of these things, like we've seen cases of that peripheral nerve disease like Guillain-Barré Syndrome, we've seen cases of de-myelination that look like what's called acute disseminated encephalomyelitis, which we know can follow other viral infections. In children, we've seen, rarely, fortunately a very severe multi-system inflammatory syndrome and all of those are things that are examples where we think the immune system is playing a key role. And it probably is, as well, in some forms of encephalitis or encephalopathy, where these patients have tremendously elevated levels of pro-inflammatory cytokines that seem to be contributing to some of the nervous system dysfunction.

Dr. Wilner:
Well, since we're talking about autoimmunity, I'm gonna jump way ahead here and, there is this whole classification of autoimmune diseases, like rheumatoid arthritis, and multiple sclerosis where, presumably, the immune system is attacking the body, and these are chronic. Now, everything we've talked about so far with SARS is acute, you know, monophasic. Is there any suggestion that this hyper-immune response is of long duration or could continue for weeks, months, or years?

Dr. Tyler:
That's really a great question, and you know, I think one of the things we certainly have recognized at a clinical level is that there's a subset of patients who had acute COVID-19 induction and as opposed to resolving that acute infection quickly seem to be complaining of a large series of, you know, chronic symptoms including those that can involve the nervous system, from headaches to alterations in cognition, to other things. And again, not exclusively a nervous system disease, but with components of it, including components that resemble things like we've seen before in chronic fatigue syndrome or some of the other related disorders. But what we don't really yet know is whether the link is that continuing activation of immune responses beyond the acute phase or not. I think we just know that this is a virus that does trigger those immune responses and that there certainly does seem to be a subset of patient's whose symptoms don't resolve quickly. Now, whether or not the immune system is the link or the causal agent, there is gonna require more study.

Dr. Wilner:
I spoke yesterday with Dr. Jennifer Frontera, NYU, and I'm sure you are well-acquainted, and she is one of the leaders of a national databank for COVID patients, where they're collecting case reports, but also body specimens to try and understand sort of, the domain of infection, you know, what happens to people? So, this is a national program and they're soliciting case reports from all physicians, academic and community physicians and samples, they're willing to store them or you can store them at your own site. People will publish, you know, three cases here, five cases there, but we really need to look at sort of population effects to begin to answer these questions.

Dr. Tyler:
Most of the original reports, especially the neurologic complications of COVID, you know, of course, tended to be from things like a single city or a single hospital and often looked only at certain spectrum of patients; maybe those that were sick enough to be hospitalized or even in an ICU. And until you start to get larger population-based studies, almost from a whole country or a whole region, it's really difficult to know the exact incidents or frequency of these different complications. And I have to admit, I think Europe's been a little ahead of us on this where they have a number of country-based registries and things where neurologists and other physicians can add cases and there've been some other kind of population-based ones. But I think you're totally right that until we start to get really high-level epidemiologic data, it's gonna be hard to know that exact frequency of many of these complications, including some of the chronic ones we were just talking about.

Dr. Wilner:
Yeah, so let's talk about what do we know now? What are the neurological complications caused by COVID-19 that we've already seen?

Dr. Tyler:
Yeah. I think I tend to put them into a series of piles. My first pile would be where the nervous system is infected indirectly by a severe COVID infection that results in multi-organ system dysfunction and often a hypercoagulable state with features of things like disseminated intravascular coagulation and so that group of patients, not surprisingly where they have respiratory involvement, cardiac involvement, occasionally liver or kidney involvement can develop, altered mental status and encephalopathy and that can be associated with sort of distinctive MRI lesions, as well. I think we also know that that hypercoagulable state is probably contributed to strokes in COVID and we've seen strokes both in older individuals with classic risk factors for stroke in which this seems to be sort of an add-on risk factor, but also in younger individuals who don't have dramatic risk factors and, again, one of the linkers seems to be this hypercoagulable and hyperinflammatory state.

I guess, in my second pile, I would say there are now examples where we have diseases like encephalitis, myelitis, brain stem encephalitis and in some of those, we've been able to show that there's direct viral invasion of the central nervous system. In other words, it really is a true encephalitis where you can detect virus by PCR in the spinal fluid or patients come to biopsy or autopsy, you can detect viral antigen or viral particles. But there seems to be a very similar clinically larger group where those kind of direct studies to prove that the virus is in the nervous system, so far, are often negative and that's a group that people have been very interested in whether or not the mechanism is this hyper, active autoimmune cytokine activation, pro-inflammatory process because they have all the signs of encephalitis, abnormal MRIs, pleocytosis in the spinal fluid but we don't detect the virus, at least by the means we've been using to date. So, the question is, is there another mechanism there?

And then my third pile we, sort of talked already a little bit about, which is, I think it's very, very clear now that there's a pile of these, postinfectious or para- if they occur closer to the actual time of the acute infection, para-infectious immune mediated syndromes. And I think the most important ones we talked about for sure include things like Guillain-Barré syndrome or its variance, or this de-myelinating syndrome that looks a lot like ADEM but there've been a number of others reported including that pediatric multisystem inflammatory syndrome.

Dr. Wilner:
Wow, so, we're learning an awful lot very fast about how this virus attacks the body and we have a lot more to learn. For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD, I'm Dr. Andrew Wilner and I'm speaking with Dr. Ken Tyler about the neurological impacts of COVID-19.

Well Dr. Tyler, we were just talking about all the different ways the virus can affect the body. Why is it that some people just fly through this and you know other people are on a ventilator and sometimes don't even survive?

Dr. Tyler:
That's a great question and I think it's still one of the mysteries of the disease. I mean, we certainly know that there are some risk factors that are common to other infections, including the fact that this is one of those viruses that infection typically is more severe in older individuals and I think it's also, perhaps not surprising, given some of the things we've talked about that there are certain underlying conditions including likely things like diabetes or hypertension that can worsen the infection. What we don't know yet is whether there are genetic predispositions and that's an intriguing field for virus infections of the nervous system, you know, more generally that there are examples, including for things like herpes, encephalitis, and West Nile, just to pick a few examples, where we know that there are host genes that seem to determine the severity of disease. And often they are linked to things like innate immune responses, so think cytokine pathways or interferon signaling or things like that. And it remains to be seen if we'll be able to parse out some of those to explain, you know, the cases that are so striking where a previously healthy, young person who doesn't seem to have any of the risk factors that I just mentioned, develops terrible and, at times, even fatal disease. And again that's something we're going to need more studies of post genetics and other things to determine.

Dr. Wilner:
Yeah, in my town, I live in Memphis, Tennessee, we just had a 36-year-old surgeon die of COVID and he was otherwise healthy, as far as we know. So, obviously there's some predisposing factors and I'm just going to say this outright because I think it's sort of, in the subtext, but I think it's worthwhile saying that as complicated as all of this is, it's not just for our sort of academic curiosity that we are striving to understand the mechanisms, it's because if we do finally understand the mechanisms we may be able to come up, not only with preventive measures and we'll talk about those later, like vaccines and mask wearing, but actual treatments that once someone does get infected, an effective treatment, just the way we have penicillin for bacterial infections, that we might actually have a pill or an intravenous treatment that would really make a difference. All the ones we have now that have been FDA approved, they're sort of marginally effective. They gotta look really hard at the results to say yes, in this subset of people it was a little bit helpful. But once we understand what really happens with this virus we may be able to come up with a treatment that that really works.

Dr. Tyler:
I think that's a great series of comments, Andrew. Usually when we think about this, we try to think about if we understand how a virus infects and replicates in cells, we can develop drugs that target key steps in that process and that's been a very successful strategy for things like herpes, encephalitis, or HIV infection and so there's the antivirals. And if we understand how a virus, say, kills cells or activates the immune system, we may be able to target very specific steps. And there are already trials of inhibitors of some of those pro-inflammatory cytokines that we talked about.

And finally, if we understand a little bit we talked a lot about the immune system, if we understand the specific parts of the immune system that are critical in control of or clearance of a virus that helps us with just what you alluded to which is both vaccine design and, of course, another whole category of therapeutics here are either things like convalescent plasma or combinations of monoclonal antibodies directed against the spike protein. So the more you understand, the more rational your design can be, otherwise you're a little bit stuck in a very empiric model where you have to, sort of, throw all sorts of random things at something and then try to do the studies to show whether or not they work. And that was, I think, one of the plagues of the early days of the COVID epidemic were a lot of things were touted as potentially effective that turned out not to be and that really had very little scientific basis for even considering them.

Dr. Wilner:
Well, I think we're out of time. Is there anything else you'd like to add before we close?

Dr. Tyler:
No, I think except just to maybe do an infomercial and say to encourage people to continue to practice physical distancing, mask wearing, hand washing, 'cause that works against all of these viruses, and if you don't get infected, you're not going to get hospitalized, intubated, or die. And I would, again, encourage if there is a vaccine available in your area, get it. Don't worry too much about which one it is, get the first one that you can and don't worry too much about the variants because if we need to develop boosters or a new vaccine or additional vaccine shots, those will come along. But it's almost certain that the existing vaccines will, at least, provide partial protection even against these new virus variants.

Dr. Wilner:
That's a great way to round out our discussion on what we currently know about the neurological effects of COVID-19 and how to prevent them. I want to thank my guest, Dr. Tyler, for joining me. Dr. Tyler, it was great having you on the program.

Dr. Tyler:
Thank you so much for having me.

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