Responses to Participants' Questions

This document provides responses* to questions raised by webinar participants related to the following presentations:

- **Presentation 1:** ***Peripheral Nervous System Involvement***
  Melissa Cortez, DO and Maria-Alejandra Gonzalez-Duarte, MD, PhD
- **Presentation 2:** ***Adult Central Nervous System Involvement: Neuropsychological and Neurological Testing and Brain MRI***
  Sudha Seshadri, MD
- **Presentation 3:** ***Psychiatric Symptoms and Issues Associated with the COVID-19 Pandemic***
  Richard Gallagher, PhD

* Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q1. Does the small nerve fiber neuropathy (SFN) impact balance simply by not being able to feel the feet and proximity as well?

Response:

Dr. Gonzalez-Duarte: No, usually not. When we are talking about balance problems, we have more information than what the small fibers are relaying. We have sensory nerves as well as proprioception, so that will be more important to balance, and those are larger fibers.

Q2. What is the benefit of SFN testing? Is there treatment available for this condition? Or is it more of just explaining/validating the symptoms and providing subsequent conditions to monitor for development as a result of SFN?

Response:

Dr. Gonzalez-Duarte: The most important thing that neurologists and people who are dealing with these conditions should know is that the most important part of treatment is getting rid of the factor that is causing the small fiber. With conditions that are metabolic, that's really easy, because you pinpoint the condition, particularly the endocrinology factors or if there's a toxin/vitamin, whatever is impairing the function of the small fibers. By getting rid of that factor, the patient improves quite well. In post-infectious small fibers, we still don't know if it's only time that will recover those nerve fibers, or if we'll have to do something. That is why they are looking into all of these conditions and therapies to see if we can decrease the response that the body is doing that is

continuously damaging the fibers. That's why I'd say that we'll have to wait a little bit to see if they'll recover, because it was a highly infectious disease that triggered an inflammatory reaction and that's why they were damaged. Or if it is something that is ongoing, then we'll have to do something else like trying these immunotherapies.

Q3. Can you elaborate on "documented cognitive impairment?" What tool was used for this?

Response:

Dr. Gallagher: The measures used to study cognitive impairment in the RECOVER project depend on the level of investigation. There are three tiers, and in the beginning the cognitive impairment is reviewed through a number of different questions about the nature of what the person is experiencing: are they having problems with memory, focus, language? At tier 2, things begin to change with regard to people actually being administered instruments, which are relatively brief, that ask them to complete tasks. Many items are taken from the NIH "toolbox." These tests are short screening measures of attention, memory, language processing and language use, and problem solving. At the third level, people are getting individual testing with neuropsychologists conducting evaluations that were presented on one of the previous slides. These may include measures from executive function tests or language expression and reception tests. These specific neuropsychological tests tap into different functional areas. For other studies that have been completed by researchers around the world, tests that have documented cognitive impairment have asked subjects to pay attention to auditory and visual details, to engage in planning actions to solve problems, to use language and to understand language, and to learn and recall visual and verbal information.

Q4. What do we suspect is the cause of dysautonomia, myalgia, insomnia, etc., in patients without SNF or diabetes and without peripheral neuropathy?

Responses:

Dr. Seshadri: I want to point out that we do know that in addition to peripheral injury, there are probably changes in central autonomic areas as well. We talked about areas like the insula and about the studies looking at the structure in the brainstem called the locus coeruleus. We know that sometimes sleep changes, for instance, can be secondary to changes in the brainstem. Even changes like shortness of breath do not always have to be because of injury to the lungs. However, a direct correlation between individual patient symptoms and changes in the brain is something that is being looked at, but it is hard to pinpoint at a single patient level.

Dr. Gonzalez-Duarte: Absolutely. I will add that for other post infectious diseases, the hypothalamus is very unique in how it manages circulation. It doesn't have the encephalic blood-brain barrier that protects other parts of the brain. Therefore, it is very sensitive to all of these changes, and particularly to the reactive/inflammatory factors.

So, if there's an extreme infection, it shows up afterwards. We see this very often in patients who have been checked into the ICU, who sometimes have trouble controlling heart rate, blood pressure, or other autonomic manifestations because of that.

Q5. One critical issue when clinicians are establishing the diagnosis of PASC is to determine if COVID-19 is really responsible for the neurological disorder or it is simply unmasking a neurological disorder. In the case of cognitive decline, what tools would you be using to establish such possibilities? Is the cognitive problem just an unmasked pre-existing dementia or is it really a post-COVID-19 cognitive decline? The same question may apply to peripheral neuropathies.

Responses:

Dr. Seshadri: This is obviously a challenging issue. One approach would be comparing an equal number of controls (similar age, sex distribution). In RECOVER, we are looking at things like an MRI in a subset of people, and there are patterns of change in MRIs that are most suggestive of a certain underlying pathophysiology. Even more valuable, we will have plasma and CSF (cerebrospinal fluid) biomarkers of things like amyloid: when you have more amyloid in the brain, you have lower levels of ab-42 in the CSF, you have measures of things like certain types of phosphorylated Tau, like p-Tau-181, 217, 231, that seem to correlate with amyloid deposition in the brain, and certain specific ones also with tau deposition in the brain. So, if those levels were high early on, one could expect that this wouldn't have happened over a 3-month period, but rather was reflective of an underlying long-term process. The fact that you're able to get serial biomarkers could tell us whether these changes change over time. There are, for instance, markers of neuron injury, like neurofilament light, that others have looked at and said that this happens soon after. One of the advantages we have are the Alzheimer's disease research centers, where these markers have been looked at in people who are normal, in people with MCI (Mild Cognitive Impairment), in people with Alzheimer's, before they had COVID. Similarly, in studies like UK Biobank, where we have a baseline level, you'll then be able to define whether the changes happening are correlated with these markers that we think are specific to neuro-degenerative processes. It's likely there's a little bit of both. Any acute illness can unmask underlying cognitive challenges. There may be some people in that domain. Whether the disease itself accelerates that process is something that'll take more time to answer, because the virus has only been with us for a couple of years. there are studies of things like brain Amyloid Tau that may give answers over time, not just blood and CSF, but also PET imaging.

Dr. Frontera: There are prospective, longitudinal cohorts that are participating in RECOVER like C4R. These had years of data and testing before these people had COVID, and there are substantial proportions of patients that

will be in RECOVER. So, we'll have at least a subpopulation that we know whether they did or did not have preexisting dementia. The same UDS factory that they're using in RECOVER is being done as part of NAC pre-covid and post-covid, so the focus there is ascertaining whether someone was infected with covid. Same as in C4R and other studies where the cognitive/MRI data is available in framing other studies. Thanks to efforts like this, we are now using questionnaires and dry blood spots to see who among this longitudinal cohort did develop infection and who did not.

Dr. Gallagher: Persons are asked to describe their experiences before and after the time that they were infected with COVID. For the time before their COVID infection, people will have to rely upon their recall about their experiences, which may have limited accuracy. However, with the large number of subjects being investigated, general trends are likely to be revealed. For the time after infection, questions will ask about many details that should reveal how health and behavior patterns have been impacted by exposure to COVID.

Q6. Is there any info on low acetylcholine levels (either directly or indirectly impacted by SARS-CoV-2) possibly playing a role especially in brain fog Long COVID symptom? That could be helped by supplementation or understanding how to address this?

Response:

Dr. Seshadri: We know that certain medications like cholinesterase inhibitors like donepezil work in a number of settings, not just Alzheimer's and MCI, but in vascular and cognitive impairment and MS. There isn't, to my knowledge, a control trial ongoing in PASC, but it's such a rapidly moving field. We know that there are a number of neurotransmitter changes that seem to be associated when we examine acute CSF. We do have both autopsy studies where we'd be able to look at gene expression, receptor levels, fluid biomarker samples to help answer that question, as well as genetic data to predict what someone's enzymatic propensity to break down acetylcholine might be. But again, I'm not aware of specific trials.

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