Transcript

Claire Kleiner

Thank you so much. Good afternoon and welcome to the Recover Research Review or R3 seminar. My name is Claire Kleiner and I'm an epidemiologist with the Recover Administrative Coordinating Center, as well as the moderator for today's seminar.

The goal of this seminar series is to catalyze a shared understanding of the research within the Recover consortium. The seminar today is not intended to provide clinical guidance. Rather, the presentations and conversations today pertain to the research realm.

Our presenters will be unable to answer clinical or treatment questions, but are well prepared to discuss and answer questions pertaining to the research in their field.

Before we move into introductions, I just wanted to thank everyone who submitted questions in advance. If you have additional questions that arise during today's presentation, please use the Q&A feature on Zoom.

After the presentation, we will answer as many questions as possible. Some of the questions may be answered within the Q&A feature on Zoom. After the seminar, we will post recording on recovercovid.org, FAQ document with the recording of the seminar, as well as answers for the submitted questions relevant to today's presentation.

Questions about other scientific topics will be addressed in future seminars and answers to broader questions about Recover will be available in the faqs@recovercovid.org. We have a great set of presenters today, which include Dr. Melissa Cortez, Dr. Alejandra Gonzalez-Duarte, Dr. Sudha Seshadri and Dr. Richard Gallagher.

I'd like to provide a brief bio of each of our presenters beginning with Dr. Melissa Cortez. She's the director and founder of the Autonomic Physiology lab at the University of Utah and specializes in neurological diseases. Her research focuses on the development and implementation of novel patient centered interventions for dysautonomia, including those resulting from post-viral syndromes.

Moving on to Dr. Alejandra Gonzalez-Duarte, she's the associate director of the NYU Dysautonomia Center and is a Carl Seaman Family clinical associate professor of dysautonomia treatment and research in the Department of Neurology at the Grossman School of Medicine. She's a medical doctor with two subspecialties in internal medicine and neurology.

Moving on to Dr. Sudha Seshadri, she's a board certified neurologist and the Robert R. Barker Distinguished University, professor of neurology, psychiatry, and cellular and integrative physiology at the University of Texas Health Sciences Center in San Antonio, where she serves as the founding director of the Glenn Biggs Institute for Alzheimer's and Neurological Diseases, and of the recently NIA designated South Texas Alzheimer Disease Research Center. She has two ongoing studies, neurocognitive consequences of COVID and leads neurology working groups within several large consortia.

Our final presenter of the day is Richard Gallagher, who's a psychologist, associate professor of child and adolescent psychiatry at the child study center, NYU School of Medicine. He specializes in neuropsychological assessment and treatment of anxiety disorders, attention deficit, hyperactivity disorders, and learning disorders. He's been a Co-PI on NIMH grants and investigating executive function deficits in children with ADHD and related disorders and how to overcome those deficits through training.

In addition to our presenters today, we have a fabulous discussant, Jennifer Frontera, who is an MD as she's a professor of neurology at NYU Grossman School of Medicine and specializes in neuro critical care and stroke. Her research has centered on epidemiology and outcomes among patients with intercranial hemorrhage, with a recent focus on the neurological impact of COVID-19.

The topic of today's seminar is clinical spectrum of PASC focus on neurocognitive function. Today's speakers, again, will share our current understanding and gaps and knowledge and how cover will contribute to filling these knowledge gaps. With that, I'd like to hand it over to Dr. Cortez.

Dr. Melissa Cortez

Hello, and thank you so much to the organizers for inviting me to speak to this audience and the privilege to review this literature. As you heard in my introduction, my clinical specialty is in autonomic disorders, but I'll focus today on peripheral nervous system dysfunction at large focusing further on large fiber neuropathic complications, and it'll be followed by Dr. Gonzalez-Duarte who will look at and share a little bit more about small fiber complications. I have no disclosures relevant to this presentation today.

So, I'm going to begin this session with a quick overview of the definitions that we use to discuss post COVID condition. And the myriad terminology used in order to introduce today's seminar of neurocognitive complications at large. Given the brevity of the segment, I won't provide a comprehensive review of all neuromuscular complications in COVID-19, but I'll focus on recent lead published high quality work that highlights how published studies have so far defined peripheral nervous system involvement, their findings, and their inherent challenges. And finally, I'll point out opportunities where current work can fill gaps, including the Recover Initiative.

So, one of the key challenges is, what do we call this and what are we studying? And there are currently numerous definitions in use. And to address this, the World Health Organization work to produce a case definition that might be usable by a broad array of stakeholders.

They use the Delphi method, which is briefly a systematic iterative survey method to identify consensus through a panel of experts. I've listed here the published definition that's paraphrased a bit for this slide, and I won't read it to you, but I want to highlight two key factors that you will hear about over and over through today's seminar.

One is the multisystemic and multi symptom nature of persisting symptoms following COVID-19 infection. And the other is the potential for fluctuating and relapsing symptoms that specifically impact daily function.

Importantly, this definition is not meant to stand alone in all time. It will be necessary and expected to refine this over time with emerging evidence, analyses and consideration of vulnerable populations and their risk factors.

A few years from now, I suspect we'll have several different definitions that might be stratified by varying pathophysiologic mechanisms as we uncover them, or perhaps by specific populations, those that are vaccinated versus unvaccinated, children versus adults.

And finally, perhaps those with different trajectories of illness or recovery, those who had a severe illness in an ICU state compared to those who had relatively asymptomatic infection, or those affected by varying variants, Delta versus Omicron or the effect of treatment interactions. So, we can expect this definition and our terminology to continue to change. But for the purposes of today, we'll focus on this post COVID-19 condition context.

So, I want to begin at this high level with a recently published survey data of a large sample of patient stakeholders surveyed by social media. The sample is predominantly female patients reporting good health before their COVID-19 infection and were not hospitalized.

And importantly, this survey data recapitulates a key feature of the World Health Organization case definition, which sets the stage for one, how we ascertain symptoms of peripheral nervous system involvement, symptomatically as well as how we're defining identification of symptoms and their impact on function.

This study in this sample reported 15% of patients had symptoms of pins and needles or sensory symptoms initially during their infection. And then 26% had ongoing pins and needles symptoms later after the infection had resolved.

Importantly, these sensory symptoms tended to cluster with other multisystemic and neurologic symptoms and what the study labeled at the minority cluster. Pins and needles clustered with poor concentration, memory problems, dizziness, confusion, which you hear a lot more about during the seminar. And importantly, this minority cluster had poorer outcomes and were more severely affected functionally in this report.

So, this sets the stage to confirm what we already know and what are key attributes of this definition. And we have to include those who had mild infection, not just those with a severe infection that symptoms can be fluctuating, can result in fluctuating or functional impairment. And that sample population matters as you'll note that there were several limitations to that survey sample and its representativeness.

So, one of the things that the Recovery Initiative will try to do is use a meta cohort approach using acute and post-acute cohorts, as well as appropriate controls and even autopsy cohorts to try to fill in some of these gaps in sampling of symptoms across a multi-systemic ascertainment, specifically, focusing on peripheral nerve dysfunction and large fiber abnormalities. We will ascertain symptoms initially like the survey did, but then we'll

follow this with a validated screen of neuropathy and standardized exams, electro diagnostics and biopsies as indicated.

So, this is stage in the pandemic. The literature is growing rapidly every day and our scope and understanding of peripheral nervous system involvement and its range is involving. This two-year review attempted to synthesize what we know so far, 169 studies and provided a narrative summary.

And the key takeaway here was that there were vastly variable estimates, up to 70% of patients reported sensory symptoms, potentially referable to peripheral nervous system involvement and pain was a very common one of those complaints. But if you limited your review to studies, relying on test based diagnoses only, the reports were much fewer, less than 10% having peripheral nerve involvement. So, we know we're dealing with some sampling bias in our current reports based on symptoms alone.

So, what can we learn from neuro physiologic testing? There are a number of very high quality reports in the literature from various single center experiences. But these again have inherent challenges. This is one of the few multi institution publications that also provides some longitudinal data. And therefore is one of our strongest pieces of data thus far, they collected 17 individuals. Again, predominantly female having reported a fairly mild infections. And over half of their sample had at least one test supportive of neuropathy with the majority of these being small fiber neuropathy, which you'll hear about in the next sub segment.

Longitudinally, they reported improvement just over half of their sample, but importantly, none had reported complete resolution of these neuropathic symptoms. If you take the literature at large, you will find a very large spectrum of neuromuscular complications, referral both to peripheral nervous system involvement.

And essentially when combined with the central nervous system complications, it representing every localization possible along the neuro axis. Almost all of these reports suffer from sample challenges, few of prospective designs and many lack electro diagnostic confirmation of the reported patterns.

So, we're dealing with a lot of sampling bias so far in heterogeneity of existing data. And that will be one key gap that ongoing studies are filling. And with this wide array of clinical manifestation, as well as neuro access localization, one of the key and most important next things we can do is arrive at a core set of outcomes that matter most in post COVID condition.

How can we reliably, accurately and meaningfully measure long term health consequences to these complications? What are the best measures to do so? Which are these complications persist or resolve? And what are the effects of treatments, viral treatments, vaccination status, or again, vulnerable populations and their individual risk factors.

So, we're learning so far based on, I think very well illustrated by peripheral nervous system, but post COVID condition at large, symptoms do not occur in isolation. They tend to cluster in a multisystemic fashion. They are associated with poorer outcomes as illustrated by an array of different measures and existing work has sampling bias and needs to advance into longitudinal data collection to answer some of these questions. That's a

key area where we'll attempt to fill some gaps, multi systemic evaluation at baseline, as well as thorough screening of risk factors and standardized diagnostic measures will allow us to fill some of these gaps followed by longitudinal data and access to real world, EHR data that will allow some advanced analyses.

So, briefly, a note on pathophysiology, in my whirlwind through the peripheral nervous system complications, I can conclude so far that epidemiologically, clinically and pathophysiologically remain uncertain and can't establish causality.

There are two main categories of hypotheses, and you'll hear more of discussion about this today, the para infectious or direct viral attack hypotheses and complications related there, and then post-infectious symptoms that come on after the initial infection and mechanisms driving those.

We had early data in that or early data in the pandemic that was promising to potentially implicate viral invasion of nociceptors, or sorry, viral invasion of neurons with nociceptors expressing ACE2 and dorsal root ganglion, or sensory neurons, but later studies have not been able to confirm that on autopsy and studies, albeit with differing techniques.

We also have a lot of temporal association with ICU related complications that are complicated by other factors that could compromise peripheral nerve function contributing to this myriad, wide range of clinical expression that we see following post COVID.

Ongoing work, and I think some of the most exciting emerging data, will be in understanding the vulnerability of peripheral nerves in people with preexisting conditions, as well as in immune mechanisms.

And finally, in summary, we know that prevalence remains uncertain. The case definitions are necessary, but limited as we try to start to characterize what we are measuring. We know that multi system symptoms cluster together and they occur in a way that we need to make sure we're measuring and not systems in isolation.

We know that post COVID condition is not uncommon and impacts those individuals with relatively mild infections. And there's perhaps in terms of peripheral nervous system involvement and emerging dominant phenotype of small fiber and autonomic involvement. And I'll turn this over to Dr. Gonzalez-Duarte to discuss.

Dr. Alejandra Gonzalez-Duarte

Lisa, and thank you for that lovely presentation. I think that I learned a lot from you. Thanks. So, let me just start the follow up of her talk [inaudible 00:16:21] to conquer. So, now I'll be presenting the small fibro neuropathy, which is a little more difficult sometimes to assess, recognize, diagnosed and, of course, treat.

So, just as an introduction, recovery from SARS-Cov-2 infection leave a tale of patients with various long COVID symptoms. And we all know, and that's why we're here. However, those symptoms that are really unspecific such as the fatigue, exertional intolerance, or that are mostly related to dysautonomia or to sensory abnormalities are difficult to assess. These symptoms may be linked to incident polyneuropathy, particularly the neuropathy that affects the small sensory and autonomic small fiber axons.

Small fiber neuropathy is a neuromuscular condition that is characterized by tingling, numbing, inability to feel temperature or pain and neuropathic pain. It may be associated with many medical conditions and the most common one is diabetes or prediabetes. And those things can be risk factors of the patients that are developing this after COVID.

It is a challenging diagnosis due to the difficulty plus a small fiber sensory and autonomic nerves. Small fibers rely sensory information of pain and temperature from the skin up to this central nervous system. In the organs, these small fibers also regulate the autonomic function, such as heart rate and deep breathing among others.

Small fiber neuropathy symptoms are primarily sensory in nature, and in opposition to the large fiber where some patients may have anesthesia, these patients usually have positive symptoms such as pins and needles, pricks, tingling, and numbness. Some patients may experience also burning pain or cold, an electrical shock like brief painful stimulus.

The important of these diagnosis is that do not involve large sensory fibers, which are basically the ones that we evaluate with the common neuro diagnostic tools such as nerve conduction velocity. Also, because the large fibers are not involved, these patients usually do not have muscle weakness, problem balance, or other things that are more easily assessed in the clinical practice. Symptoms, usually starting the feet and they progress upwards. However, in advanced cases, they can also affect the arms, the legs, the hands, and the torso.

Diagnosis is basically done with the clinical history and examination, and sometimes supported by laboratory investigations if we are available to have access to them. The most important thing for doing the diagnosis is screening for associated clinical conditions.

Electromyography and nerve conduction studies tend to eliminate the involvement of motor and large sensory fibers are useful. However, they won't give us the diagnosis of small fiber neuropathy. Nerve and muscle biopsies are rarely needed. Skin biopsies, however, have been useful, improving the decrease intraepidermal fiber density, and it's a gold standard actually of this diagnosis. When autonomic symptoms are seen, autonomic function testing also will be useful to assess these patients.

Now, what is going on in terms of small fiber neuropathy and long COVID? We have two different studies. This one is made in Boston by Dr. Oaklander. She analyzed cross sectional and longitudinal data from patients who have the diagnosis of long COVID and they were assessed 90 days after having COVID symptoms. And these symptoms lasted for more than two months.

These patients, and this is a very important thing of this cohort, I think they did not have prior history of neuropathy and they did not have risk factors for neuropathy. And that's why they were referred to evaluate. There were 17 patients in the cohort. The mean age was 43 years old, 69% were female, 94% were Caucasian and the rest were Latino population. And the studies that were done in these patients were skin biopsies in 63%, electrodiagnostic studies for small fiber in 17 and autonomic function test in 50%.

Results were that these patients 59 had at least one test confirming small fiber neuropathy. So, it's a rather large prevalence of this condition in these patients. 60% was proven with a skin biopsy, 50% with autonomic functioning tests and 70% with these specialized electro diagnostic tests.

So, with this study, we can conclude that some patients, almost more than half of them, may have infection. And after the infection symptoms and tests that are positive for small fiber neuropathy, but most importantly that most patients in this cohort had mild symptoms of SARS-Cov-2, which is also important. I think because we think that the long COVID might be related to the aggressivity of the infectious disease, but it was not the case in this series.

Now, we have another one which was done in Mount Sinai. This was a study retrospective between May 2020 and May '21 patients also with SARS-Cov-2 infection and painful parasthesia and numbness. They all went into nerve conduction velocities, and the studies show negative results. And therefore, they studied further to see if they could have the diagnosis of small fiber neuropathy. These were 13 patients, eight were women, 38 to 67 years old, three had preexisting, but controlled neuropathy symptoms and signs. So, that's why I say this is a little less poor cohort, but this is the population that we see because as I told you, diabetes is really common cause of small fiber and some patients do have it. And two patients had autonomic dysfunction by testing.

So, of these 13 patients, six have a small fiber and neuropathy confirmed by skin biopsies. Of these six patients all had suggestive signs and symptoms. Two had also autonomic testing, concomitant autonomic dysfunction, and one had severe and one moderate and the rest had the symptoms of COVID-19 mild. Seven patients had normal biopsies and one have abnormal biopsy, skin biopsy, but abnormal autonomic testing.

So, in conclusion, again, half of the patients have corrugated small nerve fiber after COVID-19. And a small fiber neuropathy may be something that underlie the parasthesia associated with long-haul COVID. However, as I said, symptoms are not predictable of who will develop this disease.

So, to be determined, and I think that's the main issue of why are we here is, who should be tested for small fiber neuropathy after COVID-19 infection and how aggressive should we be doing it, or after how much time that they start having these symptoms should we be testing those patients? So, that's why we are having this multicenter, acute study to understand better the indications for these studies.

Also, I think one of the questions that will answer this study is, if symptoms that are quite on specific, such as chronic fatigue or other autonomic symptoms are related to small fiber neuropathy, what is the response to the current treatments for pain control in patients that have small fiber neuropathy due to SARS-Cov-2, and what is the prognosis? And with that, I finish my presentation and I would like to welcome Dr. Sudha Seshadri.

Dr. Sudha Seshadri

Thank you. You've heard about PASC from the excellent prior presentations and the peripheral involvement. And I will focus a little on PASC as it pertains to brain symptoms. We know that post-acute sequelae

of COVID include symptoms that we believe would be arising from injury to the brain, the brain fog, the sort of challenge with memory, with planning complex tasks, a general feeling of slowness.

And importantly, in some studies like Goralnik about 50% of the people do not have a documented evidence of COVID acute infection, because perhaps they were affected very early on when there was not yet widespread testing.

We recognize that the duration of these symptoms vary. So, there is a lot of interest in the pathobiology and as for the peripheral nervous system, the two main theories are either virus related, which was the initial suspicion. And more recently the belief that this is, again, immune inflammation related.

The Recover strategy will try to get a comprehensive assessment of some of the symptoms we discussed, as well as brief and more extensive cognitive assessment of these domains, including memory and planning, as well as language.

And then for a subset of persons and controls actually look for structural injury in the brain with detailed MRI, with and without contrast, the contrast permitting us to look at inflammation within the brain or in the meninges. And if that is present, go on to do a lumbar puncture and examine the cerebrospinal fluid.

You already heard some discussion of autonomic function in prior R3s. And later today you'll hear about mood behavioral and psychiatric changes, but brain function also involve smell, hearing, vision, and of course, looking at the brain at autopsy, but those will not be something I'm discussing today.

Earlier this year, the NINDS had an ADRD summit. ADRD refers to Alzheimer's Disease Related Disorders, and broadly involves everything that can be considered adult neurocognitive disorder, major or minor. That is an adult who then has an acquired challenge. So, it is not synonymous with Alzheimer's disease, and this is important to understand.

The various priorities established for the next five years were to establish a research infrastructure, prioritizing disproportionately affected populations like racial and other minoritized, and understanding enough for clinical trial readiness. Recover addresses this by assembling a cohort of people who will be followed longitudinally and with good representation of race, ethnic and geographic groups.

The second priority was to define the clinical phenotype and diagnostic criteria for this subset of adult neurocognitive disorder. And what we are doing is having a fairly comprehensive assessment of symptoms and function so that over time, we can assess the type and severity of symptoms and what happens to people on follow up.

Because some controls are examined as well, we'll have some idea of how frequently this happens, the prevalence. Very important to recognize that just as whether or not one has severe COVID depends on a range of social, structural and systemic factors, comorbidities such as diabetes and smoking, medical interventions, and can depend on things like access to healthcare and access to health policy issues like availability of family leave and caregiver support.

Recover is collecting data on a range of biological, social confounders, effect modifiers, and has the potential because the data collected are similar to data collected by other efforts like R01 grants and by the Alzheimer's disease consortia, as well as long term follow up of acute clinical trials and acutely ill patients. We'll be able to pool data addressing this cognitive aspect. And, of course, we need to understand the basic mechanisms so that one can do appropriate intervention and therefore Recover will examine CSF bio and plasma biomarkers, genetics, and autopsy.

The initial thought was that since other coronaviruses could affect the brain and since anosmia is an early sign in really three things, head trauma, Alzheimer's and Parkinson's. There was concern about virally mediated neurodegeneration. We have seen after the last flu pandemic of 1918, the emergence of a delayed post encephalitic Parkinsonism, which then declined as these people died. So, there was a concern about trans-synaptic transmission, but when you look at autopsy or in CSF, you find that the virus itself rarely is seen and rarely persist. So, it's emerging that this may be because of endothelial injury or virus, secondary immune inflammatory mechanisms.

The virus seems to impact platelet and endothelial function activation resulting in fibrinogen leaks, attraction of perivascular lymphocytes, microglial activation and through a range of mechanisms, including excitotoxic damage, it may result in neuronal injury, and this in turn can then result to the cognitive symptoms that we spoke about.

There seem to be some interaction so that certain people are more susceptible. We know that people with dementia are about three times more likely, particularly African Americans with dementia to have COVID. Are they also more likely to have sequelae of COVID? And is this just because people with dementia did not do the social distancing and other precautions, or because they were in nursing homes where virus transmitted faster?

There seemed to be some biological reasons. For instance, in this finished study, about 3000 cases were compared to controls from a population cohort and persons APOE was overrepresented in the cases and more severe disease was seen in people who were E4 positive.

Another gene called OAS1 that determines whether microglia and macrophages are more responsive to amyloid. Removal of amyloid by microglia may be good for you, or whether they're more responsive to interferon that is more susceptible to immune injury. So, people with more interferon responsive streaming of the microglia may be more likely to both have severe COVID as well as a higher risk of Alzheimer's.

So, in Recover, what is our protocol? There is a brief neuro quality of life cognitive function. And if people score less than 25, there is a smaller battery of tests, which are computerized NIH toolbox. And for those who trigger based on their performance, there are a more detailed cognitive testing, which overlaps very extensively with what is done in standard testing of older persons for studies of vascular and Alzheimer related cognitive impairment.

And then tier three is the MRI and the lumbar puncture. The NIH toolbox has tests in the domain of language, verbal and visual memory and executive function. And similarly, the complete neuropsychological testing has tests spanning all these domains.

There are some imaging data suggesting that there is real structural basis for these cognitive symptoms. In about 45 people with PASC, when you did metabolism in the brain using fluorodeoxyglucose and compare it to healthy controls, these red areas are areas of the brain where there was decreased metabolism, and persons who had greater decrease in metabolism were more likely to have symptoms of memory loss, anosmia and pain.

In this large study from the UK Biobank, where a subset of people were brought back to have a second brain MRI. And the two brain MRIs were compared for change. About half this group had had been infected with COVID between the two scans and about half of them did not, but were matched for age, sex, ethnicity. And it was noted that there was some loss of gray matter, mild but discernible in the group as a whole that had had SARS-Cov-2 infection.

And where were these changes seen? In the parahippocampal gyrus that's important for memory, orbitofrontal cortex that's important for drive and areas like the insular that's important for autonomic function. So, this is the insular, the parahippocampal and the orbitofrontal.

Now, we have some triggers, not only cognition, but a range of other triggers for having MRI within, without gadolinium. And this has a protocol that permits the kind of structural analysis. Done in the UK Biobank also looks at measures of small vessel disease because we know that acutely stroke might be a little more common.

In follow up, we think that small vessel injury may be more common. So, you had look at white matter hyper intensity in facts, and about 20% is what we expect will be the subset of Recover who has brain MRI. And when you do a lumbar puncture, you want to make sure that the sample is good for amyloid markers. So, we note whether it's done fasting and collected in special tubes.

So, these assays have not been finalized because there's some ongoing discussion about the best tau assays, the best amyloid assays but the samples are here, and we hope to have more data for you over the next couple of months. Thank you.

Dr. Richard Gallagher

I'm going to be talking about psychiatric issues and what's been found in the literature to this point, and then also the literature in terms of what we're going to be doing with the programs in Recover.

So, there are psychiatric issues and issues associated with the COVID-19 pandemic that I'm going to be discussing and going through this with regard to, again, some studies that have been conducted, and it's a sample of studies with issues that we have to take into account.

So, in Recover, we are looking at psychiatric symptoms that are being investigated in all Recover cohorts. So, that does include the adult cohort and in the pediatric cohort as well. Within pediatrics, we are dealing with both the caregivers and the children in the main cohort, children in the congenitally exposed cohort, and also children in the MISC cohort. I'm going to be talking about the adult cohort and adult literature today.

Overall, with regard to psychiatric concerns, there's a myriad of psychiatric concerns that are present. There's potential direct CNS impact of the virus in the brain. As Dr. Sudha had been speaking about things before, and then there's an addition to that. There's consequences of COVID exposure and resulting illness.

So, in some cases for person that had been exposed to COVID and have a serious condition, there's post-traumatic stress disorder and/or symptoms that are associated with post-traumatic stress disorder, depending upon the course of the illness, especially during the acute phase, and then there's psychiatric reactions to changes in functioning. So, persons can certainly become distressed and have many experiences of depression and anxiety, and some other factors, if they have a change in their functioning with regard to their respiratory functioning, their gastrointestinal functioning and some of these other areas as well.

Additionally, there's been psychiatric concerns about the consequences of the illness affecting other people. So, there are psychiatric concerns in this population of people that are being studied, who may be having grief reactions because they've lost family members, or in some cases, there may be increased stress because they've been also required to care for other people as well as we know that many of the persons that were exposed to COVID, many of their family members were exposed as well. And there may be a variety of reactions and a variety of illness states in family members. And that oftentimes people that have been exposed and then recovered, who describe long COVID, they may be also experiencing stress while having to care for other people in their families.

And then finally, there have been a lot of discussions or concerns about the public health responses to the outbreak in both COVID-exposed persons, as well as controls. Throughout the world, there's been responses to increased isolation that have been put into place because of restrictions for travel and also encountering other people. There's been responses to what's been described as increased societal anxiety, that the society, as a general, has been concerned about this pattern. And this is a pandemic that has affected everybody.

And then there's responses to changes in economic status. Many people, because of the illness or because of restrictions, have had to change their economic situation and have had to respond to some of those big changes in regard to their work and their ability to support themselves.

So, with regard to these myriad of psychiatric concerns, this is a simplified version of the analysis that's likely to be multivariate. And we need to be taking a look at a variety of different things that result in a path that talk about the psychiatric symptoms when considering all these different variables.

With regard to understanding information about what has been studied so far, we're going to talk about a few different studies that have been conducted. Most of the studies that I'll be looking at will be studies that have been looking at reviews of other studies. Some of them are early studies.

Very early studies during the initial outbreak in late 2019 and early 2020 were ones that did look at primarily retrospective reports with self reports provided by people. And these are based upon persons that were hospitalized and information was gathered soon after they had obtained the infection.

Rogers et al. in 2021 did talk about in the average of a collection of studies, the depression was reported in 23% of persons in this different samples with a range going from 12 to 42%. Anxiety was reported in 16% average persons with a range between 6 to 38. And there has been a number of conditions that they did report that were more prevalent than anxiety and depression, but certainly could have an impact on emotional functioning.

The top five conditions that were reported were weakness, fatigue, myalgia, sleep disorder, and headache. And it is believed that many of these experiences could be things that contribute to the depression and anxiety that's been present as well because people were not functioning so well because of, again, weakness and fatigue or also pain.

Klaser also conducted a study in 2021 that information gathered between February of 2021 and April of 2021. And this did take a look at a number of persons that were sampled and tested for COVID exposure. And there were 413,000 persons, 270,000 people were ones that did test positive in the reviews. And it was found that they did investigate anxiety and depression.

And post COVID, the person that did test positive had a depression and anxiety rate of 31% versus 26% with indications that this sample of anxiety and depression that is often considered together was quite high in the background, even within persons that were not positive. And as we know that those persons might have had COVID because the testing might have missed them. But again, we do know that there's a high level of depression and anxiety in the background during this time of the pandemic, in these two time period.

Some other early studies, and again, this is a sample, was one that was conducted in 2021 that reviewed 51 studies. Within these 51 studies, the most prevalent concern was, again, sleep disturbance present in 27%, fatigue in 24%, and then documented cognitive impairment in 20%. Anxiety was the fourth highest concern present in 19% of people that did report to these studies. Now, again, the methods for data collection, each of these 51 studies was different, but they did work on summarizing this work to be able to indicate that anxiety was a prevalent concern.

Schaefer et al. did a study of a meta analysis of 36 studies, and this found rates of anxiety, depression, and eating pathology at pre-COVID and in the midst of the COVID pandemic in this large scale sample. When looking at things, they did find that with regard to pre-COVID time, anxiety was present in people at a rate of about 8%, but in the peri-COVID time period, when COVID was being active, it was 20%. With regard to depression, we have a

little bit over a double comparison between pre-COVID to post-COVID with 7.5% changing over to 17% during the time of the pandemic being active.

And finally, with regard to eating pathology, there was a 12% pattern in issues before COVID and changing to 21% post-COVID. And this next slide does show a little bit of a graphic of this information indicating how these things were changed when the COVID was present. And again, this was not necessarily persons that had been infected, but this is in general, what was present in the population overall of the sample that Schaefer took a look at.

Lately, there's been some post-acute samples, and these are samples in which persons that have not tested positive, again, after they did have the condition, this was a collection of persons that were not acutely ill. They did have negative PCR tests. And again, we do know that that's something that can happen, even though people might have been infected previously, but these were patients that were no longer testing positive, and depression and anxiety was reported in over 20% of the studies that were looked at. So, 20% of the studies reported rates of depression that was higher than 30%.

So, again, many of these studies did indicate very high rates of anxiety and depression. The pattern that they found was that anxiety seems to diminish in frequency with time. That anxiety doesn't seem to last, but depression in many of these studies has been documented to linger for a good number of people.

In some studies, this is an important issue, the levels of depression, anxiety in some of these studies was not higher than background levels of these symptoms in control groups, people that did not have any exposure, any documentation.

When looking at PTSD, the comparisons between controls and those that were exposed with 7% to 42% and the background level is usually about 7 to 10%. So, there's a variation that's present in all these studies, but it looks at the high level, PTSD symptoms are present in about four times the rate of what you usually expect in persons that just have different experiences that result in PTSD in daily life.

Another sample conducted in 2022 looked at 33 studies. Again, that were patients that were not actively ill. And they found that anxiety was inconsistent across studies and indicated and concluded that things were mostly short-lived for most people with regard to anxiety.

Again, in this sample of studies, depression was not significantly higher than background rates. And again, they also found that PTSD was not higher than normal in terms of comparisons of persons about so. Again, we have some information here that indicates that these psychiatric reactions may not be very different than what's going on because of exposure to COVID and the COVID restrictions.

Another study found that, again, anxiety and PTSD were not more prevalent than in a controlled group. However, depression was found in 26% compared to 17% in controls. And it was postulated that COVID illness severity seems to be correlated with increased endorsement of psychiatric symptoms.

So, when people were surveyed and provided information about the experience that they have with COVID with regard to being treated on an outpatient basis, with regard to having severity of symptoms when it was active and also when being hospitalized, it did seem that then when the more severe the illness, the more likely there was an increased endorsement of psychiatric symptoms.

And in summary, we have this situation that based upon prior research, we would think that anxiety is likely to be prevalent perhaps only in the first months, as a possible pattern and conclusion. Depression is likely to be prevalent with indications of persistence throughout some of the studies. PTSD symptoms that include anxiety and depression are likely to be prevalent in those that were hospitalized, and especially those requiring ICU treatment. And this was found in a number of studies, but some studies didn't indicate this. So, it's not necessarily a pattern that is consistently indicated.

Psychosis has been reported at a higher rate than usual under a typical circumstances. And there's also some indication that obsessive compulsive disorder is present in more persons than is typical. As was indicated earlier in the prior study, the mechanisms for change are not well understood. Candidates include increased inflammation of the CNS tissue. And it's also not clear in some studies with regard to psychiatric patterns if COVID-19 is neurotoxic, and what's important is, comparing to control groups with limited exposure is really very critical just because of the unusual nature of what was going on in the world in general.

So, the questions for Recover are several. One is, what are the high frequency symptoms among long-term COVID subjects? And what are the patterns? Is anxiety and depression, and some indications of PTSD, really something that we need to really be very clear about understanding? We want to understand how do these frequencies compare to background symptoms. Again, those are present in the population at large.

And when there are heightened psychiatric symptoms, there's a number of different questions that are being asked. What factors contribute to this? What symptoms can be linked to evidence of CNS physical damage and changes that are present? What symptoms can be linked to this illness experience? Again, with regard to the severity of the illness that people are experiencing. Or if persons are close to death or really seriously ill, does that illness experience result in more psychiatric symptoms for those persons?

Again, what symptoms can be linked to diminish functioning if persons are having other symptoms and other patterns of concerns with regard to their respiratory functioning, with regard to fatigue, with regard to brain fog, what reactions are there psychiatrically to having those changes and functions? People's lives have been altered significantly, and they might end up having a lot of discouragement and dysphoria because of that.

Again, in addition to this, and this is especially true with regard to adults as well as kids, what symptoms are linked to COVID restrictions in family, social and work lives? What happened because of isolation and restriction? What symptoms can be linked to grief and stress over illness and significant others? And also does the bodily response to illness contribute to symptom, frequency and pattern? In other words, if there is found to be

increase in cytokines and inflammation that would be evidence that provide issues in the central nervous system. Is that related to symptoms that are psychiatric as well?

And finally, one of the things I wanted to be able to point out was the concern of the neuropsychiatric committee, was the concerns with regard to making sure that things were reviewed at the different levels, tier one, tier two, and tier three for serious psychiatric issues. And what's being done with regard to concerns about suicidal ideation.

What's been concluded within the group is that screening for serious psychiatric symptoms is critical. And it's critical at the very beginning of tier one. There were efforts made to be able to make sure the screening strategies are established and that there's follow through to be able to make sure that people have an understanding of what they can do if they are experiencing these patterns, and suicidal ideation and thoughts of being better off dead are being reviewed in the first response.

And when that's happened, patient participants did say that this topic was crucial. There was some concern within the neuropsychiatric group, if this should be actually investigated. But patient advocates did say that they thought that this was really important. Psychiatric specialists also said that this was really critical to be reviewed.

And the method for screening was thoroughly debated and investigated. And altogether, there were some triggers that were selected for individual follow-through where a person that are responding are getting a prompt to indicate that they can do something if they're experiencing this and that they should follow through with their healthcare provider or their mental health provider, if they have that.

And in addition, then there's been a sequence of steps that include that screening questions that are selected, that are most sensitive and alert is sent to the subject for taking steps. And then there's an in-person contact with the subject to review details through an interview by a clinician.

And during the interview, the subjects are asked to make sure that they know what steps they can be taken in their area to address this problem. And we thought that this is a really important part for people to know that this is being a consideration that's being taken into account in these initial evaluations for psychiatric symptoms. And I'm going to stop there and get us ready for being able to have questions in the panel discussion. Thank you.

Claire Kleiner

Wonderful. Thank you for those great presentations. I want to dive right into some of the questions that we've received through the Q&A to make sure we get as many people's questions answered as possible.

We'll start with you, Dr. Gallagher, since you just presented. We had a participant who wanted you to elaborate on the documented cognitive impairment that you described. Specifically, what tool is used to measure this?

Dr. Richard Gallagher

Well, the cognitive impairment depends upon 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 people are experiencing. Are they having problems with memory? Are they having problems with focus? Are they having problems with regard to use of language?

At tier two, things begin to change with regard to people actually being administered instruments that are relatively brief that do ask them to complete tasks. Many things are taken from what's been described as the NIH toolbox.

And at a third level, people are getting some individual cognitive testing with neuropsychologists conducting evaluations that were presented in one of the previous listings, so that they, for example, include full measures from some of the different executive function tests, some of the language expression and reception tests that are used to be able to understand these cognitive impairments. So, there are specific neuropsychological tests that tap into all the different functional areas.

Claire Kleiner

Thank you, Dr. Gallagher, and I apologize. I jumped ahead of myself a bit. I'd like to pass this on to Jennifer Frontera who's going to lead the discussion here. Sorry about that, Dr. Frontera.

Dr. Jennifer Frontera

No problem. Thanks a lot. So, we heard a few great talks. I'm going to summarize briefly and then actually wanted to instigate maybe a little bit of discussion amongst the panel members. I certainly have a few questions I wanted to throw at people.

So, just to summarize first, we heard a lot about the peripheral nervous system where I didn't realize that up to 70% of patients in some studies complain of some peripheral nervous system complaints, although only about 10% seem to test positive on formal testing.

And there's really only a couple of groups that have published any data, that being the Harvard group and the Mount Sinai group and really small cohort. So, I think we do need a lot more to come out on this issue. And it's certainly anecdotally something that we hear frequently in our COVID clinics.

We also heard a little bit about cognitive impairment, and this is a huge topic. Sudha did a fantastic job giving us a nice overview and really going through some of the tiers that Recover is using to try to tackle cognitive issues following COVID.

And I think it's interesting that we do actually, based on the UK Biobank data and some of the pet scan data, there's at least some imaging biomarkers of something pathological happening that's different than what's happening in control groups.

And Dr. Gallagher presented a nice overview of psychiatric manifestations or complications of the pandemic. Particularly, I like that you really called out some of the life stressors that are major factors in rates of psychological and psychiatric issues cropping up, namely social isolation, economic factors, and so forth.

And I think it's interesting that there probably is some kind of bidirectional influence. You had mentioned those five factors, weakness, fatigue, myalgia, sleep, and headache that seem to impact rates of anxiety and depression or vice versa.

And I think that having a holistic approach to long COVID is important in the sense of taking into account, not just one symptom at a time, which sometimes we do when people are referred to a specialist, maybe just going to, I might see somebody just about cognition, but it's important to account for other factors. If there's a mood issue or peripheral neuropathy, these symptoms tend to cluster. And I think having a holistic approach is important.

And I also like the fact that you should called out that anxiety and depression apparently doubled during COVID times as a background rate in the population. And I think that's important to take into account how much of this is driven by COVID versus by other factors that are occurring at the time.

I wanted to just take a minute to throw out a couple questions to our panelists, just to start with Alejandra. In regards to the peripheral nervous system complaints, what is your threshold for doing a skin biopsy on these patients?

And Anne Oaklander has actually been a proponent, who put out that Harvard paper that was presented, a proponent of using IBIG to treat these patients for immune-mediated, peripheral neuropathy. And I wanted to get your thoughts on that. Is that ready for prime time? What do you think?

Dr. Alejandra Gonzalez-Duarte

Thank you, Jennifer. I think that we have not enough evidence to jump through every single patient that is complaining of paresthesia or pain to do skin biopsies much less to start treatments like IBIG, so I would think that first we have to do the formal assessments, meaning that we have to know exactly who is the patient in terms of the risk factors they had before COVID.

Secondly, if we think that this is something new that have no other causes, therefore we cannot either get away the factor that is causing the neuropathy, then we have to start treating the patients. If we really feel that it's small fiber with the normal, regular medications that we use to see if the pain goes away and the patient gets better before we start considering a diagnostic tools like skin biopsy, which are invasive, and can give us a clear idea, object I think that it's still way after the encounter of the first round of treatment.

If so, I would think that the dedication of the skin biopsy, if we are going to do it in the regular practice will be to assess if we have to move to further treatments. That will be my aim of doing that test.

Dr. Jennifer Frontera

Okay, great. So, you would try some therapeutics first to see if they're effective before moving on to biopsy in more advanced treatment?

Dr. Alejandra Gonzalez-Duarte

Absolutely. For around three weeks to one month, see how the patient is doing or move forward into the algorithm.

Dr. Jennifer Frontera

Great. So, Sudha, I wanted to throw this at you. In last month in nature, they had this paper on CCR5, and Alzheimer's in mice, and it was super compelling because of the HIV drug, maraviroc, I'm not sure I pronounce it, that basically might have some efficacy in this.

And CCR5 being an inflammatory receptor, do we anticipate that, that might be a factor at play in cognition after inflammatory diseases like COVID? And I know we're collecting cytokines as part of Recover, has this topic come up as a potential area of investigation? You're muted, Sudha.

Dr. Sudha Seshadri

Thank you, Jen, for that question. And this is clearly a very exciting area. One of the hopes is that the study of cognitive changes after in the setting of PASC could also tell us about cognitive changes in the setting of other kinds of sepsis, other kinds of postviral syndromes as well, perhaps as something about immune inflammatory component to neurodegeneration.

Unfortunately we know, so this is very hopeful. I've looked at that paper. I've had people say, "Do we want to do phase one trials in AD?" But we know the number of medications that have worked in mice to either remove amyloid or bring back memories or reduce inflammation, and then not worked in humans because we have in the setting of COVID models, like zebrafish models, looking at the effect of the spike protein, interaction on neuropathology, you have K18 HAC, two mice that have anosmia and you're looking at, and they lose sexual interest because of the anosmia. You have these kind of assembloids.

So, there are a number of very interesting models. And that paper in nature is very intriguing. I and many others are looking at it, but I've learned to be a little circumspect in enthusiasm.

Dr. Jennifer Frontera

Okay. Cautious optimism, and that's great. And we are collecting that like CCR5, right? So, we will have some information on this. Is that something we can also test in the CSF?

Dr. Sudha Seshadri

We can, the concentrations are very low. So, I think we'd have to see, I don't know what the normal distribution, normal population is, but because we have these bio samples, I think the final list of assays that are going to be done is still influx. And there are going to be secondary grants applying to use some of these bio samples.

Dr. Jennifer Frontera

Yeah. Yeah. Some of those are already getting funded, so hopefully we'll have some more information. There's a lot of immune mechanistic pathophysiology grants that are, I think, coming through from the last cycle. So, that's great.

So, Dr. Gallagher, tough question for you, I think, as a neurologist I view anxiety, depression, PTSD, a lot of these things as neurotransmitter imbalances that are effectively biological, but there's a huge stigma against mental health treatment in many communities, also in the COVID communities. And I'm wondering how can we build bridges or deal with some of these factors that we can have a more holistic treatment plan for patients that have long COVID that have multiple symptoms?

Dr. Richard Gallagher

Well, I think that, that's always, again, a very important issue between the relationship between the healthcare provider and the person's involved. And in many cases, if people are able to say that these things are based upon neurology and then mind reacting and having low mood, I'm having some anxiety because of what's going on with my brain situation, my brain fog, I think that, that might be the entry method for dealing with things, to be able to say, "Look, we are attending to what you're saying with regard to a fatigue. We are looking at attending to what you're talking about with regard to problems with concentration and weakness."

And it's likely, could you let us know a little bit about how this is affecting you emotionally? How do you feel as you begin the day and looking forward to the rest of the day when you have these conditions, and that might be an avenue for being able to work with people and say this doesn't look like it's a psychiatric situation.

You are not crazy. We are thinking that you're responding to this strong illness and we do want to be able to take a look at the reaction that you're having. And I think that's a way to be able to work with persons that do have concerns. And when you say something is psychiatric, that it means that you're a crazy person that doesn't

have a really good touch with reality. But to be able to say that this is a reactive pattern, I think is an avenue for being able to have those discussions.

Dr. Jennifer Frontera

Thank you. Thanks to all our panelists. I'm going to turn it back over to Claire who is going to go through some of the questions we've gotten in the chat.

Claire Kleiner

Wonderful. Thank you, Dr. Frontera. I'd like to ask Dr. Gonzalez-Duarte to answer a question. Does the small nerve fiber neuropathy impact balance simply by not being able to feel the feet and proximity as well?

Dr. Alejandra Gonzalez-Duarte

No, usually not. When we are talking about balance problems, we have more information than what the small fibers are relying. We have sensory nerves and also the proprioception. So, that will be more impairing the balance, which is larger fibers than the small fibers.

Claire Kleiner

Wonderful. Thank you. One more for you, Dr. Gonzales, what is the benefit is of SFN testing? Is there treatment available for this condition or is it more just explaining or validating the symptoms in providing subsequent conditions to monitor for the development as a result of SFN?

Dr. Alejandra Gonzalez-Duarte

The most important thing that a neurologist and the people that are dealing with this condition should know is that the most important part of treatment is getting rid of the factor that is, at this point, causing the small fiber.

So, with conditions that are metabolic, that's really easy because you pinpoint the condition, particularly the endocrinology factors, or if there's a toxin or if there are vitamin or whatever is impairing the function, the small fibers, by getting rid of that factor, they will survive, they will thrive and the patient improves quite well.

In this post infectious, small fiber, we still don't know if it's only time that will recover those nerve fibers, or if we have to do something particularly. And that's why they are looking into all these immune conditions and immune therapies to see if we can just decrease the response that the body is doing that is damaging continuously the virus.

That's why I would say that I will have to wait a little bit to see if they will recover, just because it was this high infectious disease that triggered a very inflammatory reaction, and that's why they were damaged. Or if it's something that it's ongoing and then we have to do something else like trying these immunotherapies.

Claire Kleiner

Absolutely. That makes sense. Thank you. Opening it up to the rest of the panel, we have a couple of questions. What do we suspect is the cause of dysautonomia, myalgia, insomnia, et cetera, in patients without SNF or diabetes and without peripheral neuropathy?

Dr. Alejandra Gonzalez-Duarte

Is that to me?

Claire Kleiner

That's available to the whole panel.

Dr. Alejandra Gonzalez-Duarte

Yeah. I remember that. Can I ask or does someone else wants to answer?

Dr. Sudha Seshadri

I just want to point out that we do know that in addition to peripheral injury, there's probably changes in central autonomics areas as well. We talked about areas like the insular. We talked about where there are studies that are looking at the structure and the brain stem called the locus coeruleus.

We know that sometimes sleep changes, for instance, can be secondary to changes in the brain stem and even sensations 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 specific changes in the brain is something that is being looked at, but hard to pinpoint on a single patient level.

Dr. Alejandra Gonzalez-Duarte

Absolutely. Absolutely. I will add that for other post infectious diseases, we do remember that the hypothalamus is a very, very unique in terms of how it manages the circulation because it doesn't have the filter that the enkephalin, blood-brain barrier has in the other parts of the brain.

Therefore, it's very sensitive to all these changes and particularly to the storm of the reactive factors or inflammatory factors. So, if there's an infection, an infection is in a magnitude that it's really, really high. It gives all these changes afterwards.

And we see this very often in patients that have been treated in the ICU. They have different changes, including the... Or from multi insomnia to a very, very difficult controlling blood pressure or on the heart rate or other autonomic manifestations because of that.

Claire Kleiner

Thank you. Moving on to the next question, again, this is available to the whole panel. 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 if 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 preexisting dementia, or is it really a post COVID-19 cognitive decline? The same question may apply to peripheral neuropathies.

Dr. Sudha Seshadri

So, this is obviously a challenging issue. And one of the ways would be comparing an equal number of controls of similar age and sex distribution. In Recover, we are looking at things like an MRI in a subset of people, and there are things like patterns of change in MRI that are more suggestive of say a certain underlying pathophysiology, even more valuable, we will have plasma and CSF biomarkers of things like amyloid.

When you have more amyloid in the brain, parenchyma, you have lower levels of Abeta42 in the CSF. You have measures of things like certain types of phosphorylated tau, like ptau-181, 217, 231 that seem to correlate with amyloid deposition in the brain and certain specific ones, perhaps also with tau deposition in the brain. So, if those levels were high early on, one could expect that this would not have happened over, say, a three month period, but rather is reflective of an underlying longer term process.

The fact that you are able to get serial biomarkers could tell us whether these changes change over time. There are, for instance, markers of neuronal injury, like neurofilament light that Dr. Spudic and others, Dr. Frontera and others have looked at and said that this happens soon after an illness.

One of the advantages we have is that there are like the Alzheimer's disease research centers where these markers have been looked at in people who are normal, in people with MCI and people with Alzheimer's before they had COVID.

Similarly, in studies like UK Biobank, where we have a baseline level, you will then be able to better define whether the changes happening are correlated with some of these markers that we think are a little more specific for neurodegenerative processes.

So, I don't know that it's likely that there's a little bit of both. Any acute illness, particularly if somebody was acutely ill in an ICU, we know can unmask underlying cognitive challenges.

So, there may be some people in that domain, whether the disease itself accelerates the process is something that I think will take a longer time to be able to answer because the virus has only been with us for about two 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.

Claire Kleiner

Sudha, I was just going to add also that there are prospective longitudinal cohorts that are participating in Recover like NC3 that Sudha represents. So, these have years of data and testing before these people had COVID and those were substantial proportions of patients that are going to be in Recover.

So, we will have at least a subpopulation that we know does not have preexisting dementia or whatever, as well as who do have some preexisting dementia. I don't know if NAC or any of the ADRCs has anything going on, looking at controls who later have COVID. That's the thing. Are you guys doing that Sudha?

Claire Kleiner

Yeah. The same UDS battery that we're using in Recover is being done as part of NAC and pre-COVID, as well as will be continued post COVID. So, the focus there is on ascertaining whether somebody was infected with COVID same as in C4 or other studies, whether cognitive data, MRI data is available in framing MN, MESA and other studies. And thanks to efforts like this, we are now using questionnaires and dried blood spots to see who among this longitudinal cohort did develop infection and who did not.

Dr. Jennifer Frontera

Sorry. I said NC3, and I don't even know what that is. I meant CR4.

Dr. Sudha Seshadri

NC3 is some of the NAC collaborations are with NC3.

Dr. Jennifer Frontera

Oh, that's the [inaudible 01:24:27] data. Sorry, I meant C4.

Dr. Sudha Seshadri

C4R, and, of course, C4Rs of certain subset of C4R participants are having the very detailed testing of Recover soon after the viral infection.

Dr. Richard Gallagher

And what's also being asked with regard to some of the questionnaires is the ideas of comparisons that are being made between the time that a person did become infected. And beforehand, again, it's retrospective and there's issues with regard to the accuracy of that. But people are being asked questions about the nature of their pattern before this occurred as well as then afterwards.

Claire Kleiner

Wonderful. Thank you. One final question. Is there any available information on possibly low acetylcholine levels, either directly or indirectly impacted by SARS-Cov-2, possibly playing a role, especially in brain fog, long COVID symptoms that could be helped by supplementation or understanding or how to address this low acetylcholine levels? That's open to the whole panel.

Dr. Sudha Seshadri

We know that certain medications like acetylcholinesterase inhibitors, like donepezil work in a number of settings, not just Alzheimer and MCI, but in the setting of vascular cognitive impairment, multiple sclerosis.

There isn't, to my knowledge, a controlled trial ongoing in PASC, but it's such a rapidly moving field that if somebody else is aware of one, we know that there are a number of neurotransmitter changes that seem to be associated at least when we examine acute CSF.

But I think that's the best answer I have at this time. We do have both autopsy studies where we'll be able to compare gene expression, receptor levels, and fluid biomarker samples available to help better answer the question. And also some with the genetic data, you can predict how somebody's say enzymatic propensity to break down acetylcholine, maybe what are the variants of your trial cholinesterase. But again, I'm not aware of specific trials.

Claire Kleiner

I just wanted to take a moment to thank all of our panelists for being here today and sharing with us all of this great research and summaries. I wanted to thank all of the participants for their time, as well as these great questions.

Again, the questions that we weren't able to get to today, we'll do our best to get those answered and posted on the website. I wanted to remind you that this is a webinar series that we hope that you can join us for in the future. Here, we have a list of the upcoming topics that we'll be addressing in these R3 seminars.

With that, I'd like to give everyone three minutes back to their day. And again, thank you all so much for your participation.

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