International Association for

IACFS/ME

Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis

IACFS/ME Conference: Summary of Long COVID & ME/CFS Talks

The IACFS/ME scientific conference brings together top researchers annually to discuss myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) research. This conference also included several important talks on the overlaps between ME/CFS and Long COVID, which we have summarized below for the media.

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- Keynote: ME/CFS and Long-COVID: Overlapping or Distinct Entities?
- Immune Dysregulation in ME/CFS and Long COVID-19 Syndromes
- ME/CFS and Dysfunctional Breathing in Patients with PASC
- COVID-19 Symptoms Over Time: Comparing Long-Haulers to ME/CFS
- Two Symptoms Accurately Identify Post-exertional Malaise in ME/CFS

- **Keynote Address: "ME/CFS and Long-COVID: Overlapping or Distinct Entities?,"**
  Dr. Avindra Nath, MD, NIH, NINDS Clinical Director

"I think the tools we've applied to study ME/CFS can now easily be applied to long COVID as well. And vice versa. What we've learned on long COVID is going to benefit us in ME/CFS," Dr. Nath – Live Science

Dr. Nath is the principal investigator of two NIH Intramural Long COVID studies:
- Natural History of Post-Coronavirus Disease-19 Convalescence at the NIH
- An Observational Study of Neurologic Function after COVID-19 Infection

Dr. Nath is also the PI of the NIH intramural post-infectious ME/CFS study. Once the COVID pandemic lockdown hit, Dr. Nath said they stopped participant recruitment for this study and are currently focusing on analyzing the data and writing up a large paper, which will be followed up with subsequent smaller papers.

Summary of Dr. Nath's talk:

- Dr. Nath called long COVID "a huge problem and a major crisis."

- A large UK study found that COVID-19, influenza, and other respiratory infections all produced long-lasting complications, with COVID-19 producing more than the flu, and the flu producing more than respiratory infections. We should see many more studies of this size and ilk over time.

- Dr. Nath believes immune activation or viral persistence is likely the cause of Long COVID. The coronavirus could be persisting in the stomach lining or elsewhere, and it could be pumping out proteins that are activating the immune system.

- Citing a finding of "extremely aggressive monocytes," Dr. Nath suggested that T-cell exhaustion may be causing the immune system to compensate by jacking up the efforts of the early acting, highly inflammatory, innate immune system. It may be necessary to enhance the later-acting adaptive side of the immune system, while knocking down the innate immune system.

- Congested blood vessels, microhemorrhages, and white hyperintensities (also found in ME/CFS) all indicate that a complex problem involving the blood vessels is present. Dr. Nath believes damaged endothelial cells lining the blood vessels are activating the blood platelets, which then produce inflammation.

- While the impact on the brain can be widespread, Dr. Nath focused particular attention on the brainstem – a brain organ of interest in ME/CFS as well. Microglial activation there appears to be damaging the neurons. Dr. Nath has been unable to find evidence of virus in the brain.

- During the Q&A, Dr. Nath proposed that because of the vanishingly small amount of protein found in them, the coronavirus vaccines are far safer than the virus itself. He suggested that people who fare poorly with the vaccines would likely have done far worse with the virus.

- When asked if the glymphatic system, EBV reactivation, epigenetic alterations or autoantibodies were involved in long COVID, Dr. Nath said all of those are commonly found in central nervous system diseases. He warned about giving too much significance

to EBV reactivation or the presence of autoantibodies.

- The ME/CFS Intramural Study was closed with the advent of COVID-19, and no more patients will go through the study. They are analyzing the results of the study now. The results of that study will be compared with the results of the Long COVID study, which is employing ME/CFS-like patients.

* See Cort Johnson's blog (Health Rising): "A Huge Problem and Major Crisis": Avindra Nath on Long Covid at the IACFS/ME 2021 Conference" (Aug 24, 2021).

- **"Immune Dysregulation in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Long COVID-19 Syndromes: CD8 T-cell Overactivation and Exhaustion, Increased CD4+CD8+ T-cells and Aberrant Cytokines,"** Dr. Anna Gil, MD, PhD, University of Massachusetts Medical School

Intro: Dr. Gil hypothesized that Long COVID and ME/CFS are either the same disease or related diseases that result from an aberrant response to an immunological trigger (such as infection), which leads to long-term dysregulation of the immune system with overactivation of CD8+ T cells and subsequent exhaustion.

Methods: Her lab compared magnet-sorted CD8+ T cell fractions (subsets) in PBMCs (peripheral blood mononuclear cells) from ME/CFS (n=10), Long COVID (n=3), and healthy people (n=3-16).

Results: Relative to healthy controls, both ME/CFS and Long COVID PBMCs showed higher frequency of immature CD4+CD8+ T cells and lower frequency of cytotoxic CD8+ T cells (an increased CD4:CD8 ratio); both disease groups also showed lower production of CD8+ cytokines (TNFa, IFNg, MIP1b) after stimulation. Differences between the ME/CFS and Long COVID groups included ME/CFS CD8+ T cells showing greater expression of exhaustion markers and Long COVID CD8+ T cells showing greater expression of activation markers. A possible explanation for this difference in CD8+ T cell activation state is that functional exhaustion may be greater in ME/CFS versus Long COVID, as the ME/CFS participants all had chronic disease present for greater than 5 years.

Conclusion: Potential T cell biomarkers for Long COVID and ME/CFS include: high CD4+ and low CD8+ expression (altered CD4:CD8 ratio), high CD4+CD8+ frequency, and CD8+ functional studies for exhaustion.
Possible therapeutic strategies include: 1) Checkpoint inhibitors that are being used to reverse CD8+ T cell exhaustion in tumor therapy and chronic viral infections; 2) Anti-cytokine therapies that are being developed for other autoimmune conditions, and 3) Antiviral therapies. Due to CD8+ T cell exhaustion, Dr. Gil questioned whether ME/CFS and Long COVID patients have difficulty controlling persistent/latent herpesviruses, such as EBV, HHV-6, CMV, HSV, where

they are continuously getting reactivated. In addition, further research needs to investigate whether Long COVID (and ME/CFS) patients have persistent antigens (SARS-CoV-2 or other viral components/proteins; auto-antigens) continuously stimulating the immune system, which may contribute to eventual CD8+ T cell exhaustion.

- **"ME/CFS and Dysfunctional Breathing in Patients with Post-Acute Sequelae of SARS-CoV-2 Infection (PASC),"** Dr. Donna Manini, Mt. Sinai School of Medicine

Intro: Dr. Donna Mancini of the Mt. Sinai School of Medicine presented the results of Long COVID patients after undergoing a cardiopulmonary exercise test (CPET).

Methods: Dr. Mancini's study involved 41 patients with a history of a positive COVID-10 PCR test and current persistent dyspnea for more than 3 months following acute infection. Nine of the participants required hospitalization; none were intubated or on high flow oxygen. They all had normal CXR, PFTs and ECHOs results. The mean age of participants was 45.

Results: 59 % of the PASC patients had circulatory impairment to exercise, and 88 % had dysfunctional breathing and hypocapnia. 46 % of the participants met the Fukada criteria for ME/CFS.

Conclusion: Dysfunctional breathing and chronic hyperventilation may underlie the symptoms of PACS. CPET may be an effective tool for objectively identifying abnormalities associated with PASC, which can be targeted for treatment.

- **"COVID-19 Symptoms Over Time: Comparing Long-Haulers to ME/CFS,"** Dr. Leonard Jason, PhD, DePaul University

Intro: Dr. Leonard Jason investigated these questions: 1) How does COVID-19 symptomatology progress over time? 2) How do COVID-19 patients compare to people with ME/CFS during the initial phases of COVID-19, and sometime after?

Methods: ME/CFS participants (n=502, ill for at least 2 years) answered the DePaul Symptom Questionnaire (DSQ) - a 54-item self-report measure of ME/CFS symptomatology - to rate the frequency and severity of their symptoms over the last 6 months. (DSQ symptom domains include: sleep, post-exertional malaise [PEM], neurocognitive, immune, neuroendocrine, pain, gastrointestinal [GI], and orthostatic.)

Long COVID participants (n=278) took a modified DSQ twice in one sitting with the addition of CDC-recommended COVID-19 symptoms: dry cough, loss of taste/smell, difficulty breathing, diarrhea, nose congestion, loss of hair. They 1) Recalled information about their initial state of

COVID-19 (initial, first 2 weeks of infection) and 2) Answered questions on how they currently felt (current, about 5.5 months post-SARS-CoV-2 infection).

Results: Across the two timepoints, most symptoms significantly improved for participants with COVID-19 with the exception of the following symptoms: sensitivity to alcohol, neurocognitive symptoms (trouble forming words, difficulty focusing, and absent-mindedness), and loss of hair. Comparing COVID-19 vs. ME/CFS participants: At the Initial timepoint, COVID-19 participants were more impaired in the immune and orthostatic domain, while ME/CFS participants were more impaired in the GI and neurocognitive domains. At the current timepoint, ME/CFS participants were more impaired across all symptoms, except the orthostatic domain (chest pain, shortness of breath, and irregular heartbeat).

Conclusion: Several neurocognitive symptoms within the COVID-19 group got worse over time, whereas improvements occurred in most other symptom domains. The types of neurocognitive problems that are intensifying over time in some Long COVID patients might provide investigators with insights into other possible nervous system pathologies, such as that found in people with ME/CFS. ME/CFS participants in this study have been sick longer than the Long COVID cohort and, therefore, may show different symptomatologic and underlying pathologic profiles. In addition, due to the current timepoint being approximately 5.5 months after infection, Long COVID patients may continue to show changes in their symptom profile over time, either as they continue to recover or continue to progress with chronic illness, which may include a diagnosis of ME/CFS.

Published paper in *Fatigue: Biomedicine, Health & Behavior*: "COVID-19 symptoms over time: comparing long-haulers to ME/CFS"

- **"Two Symptoms Accurately Identify Post-exertional Malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS),"** Dr. Todd Davenport, DPT, MPH, University of the Pacific

Note: Post-exertional malaise (PEM) is the worsening of symptoms following even minor physical or mental exertion, with symptoms typically worsening 12 to 48 hours after activity and lasting for days or even weeks. Post-exertional symptoms are unusual in the general population, and are commonly missed and dismissed by healthcare providers due to diverse symptoms, variability in onset and duration after an exertional event, and variability between and within patients. Due to its complexity, most doctors don't even ask about it. Although PEM is considered a cardinal symptom of ME/CFS, its reliability as a criterion for diagnosis is weakened by its subjective and variable presentation. The serial 2-day cardiopulmonary exercise test (CPET) employs a controlled and standardized stimulus to induce PEM.

Intro: Dr. Davenport and his group have previously shown that people with ME/CFS are more likely *not* to recover from cardiopulmonary exercise testing (CPET) within 24 hours and that post-CPET symptom profiles could accurately classify people with ME/CFS versus sedentary (deconditioned) controls. The purpose of this study was to determine the measurement properties of post-exertional symptoms after a 2-day CPET to develop a clinical prediction rule that identifies ME/CFS. They investigated the questions: 1) Can we combine post-CPET symptoms and timing to come up with a simple measure? and 2) What is the minimum number of symptoms that tell us whether a person may have ME/CFS?

Methods: Post-exertional symptoms were measured at 4 timepoints: 1) 24h post-CPET-1, 2) immediately post-CPET-2, 3) 24h post-CPET-2, and 4) 7 days post-CPET-1.

Results: At any timepoint after the first CPET, the following self-reported symptoms were significantly associated with ME/CFS group membership: cognitive dysfunction, decrease in function, fatigue, flu-like symptoms, GI disturbance, headache, mood disturbance, muscle/joint pain, pain, lack of positive feelings/mood, sleep disturbances, and weakness. The diagnostic accuracy of symptoms (sensitivity and specificity) changed over the post-exertional recovery period. The two post-exertional symptoms that most consistently identified people with ME/CFS were decrease in function and absence of positive feelings/mood.

Conclusion: Decreased function is an important component in all ME/CFS case definitions and also a prominent feature in the peer-reviewed ME/CFS literature. Lack of positive feelings/mood is the opposite of what we see in non-ME/CFS populations after exercise. For example, increased positive mood is usually reported after acute exercise in sedentary people and people with anxiety and depression. Future directions include: 1) Validate findings in a larger and more diverse sample, 2) Determine how well clinicians can use the simplified prediction rules, 3) Consider the role of symptoms intensity, 4) Integrate objective findings after CPET, such as step counts and activities of daily living, and 5) Correlate symptoms with physiological CPET findings.

Additional Reading: Post-exertional symptoms distinguish ME/CFS subjects from healthy controls, *Work* (2020), Mateo LJ et al

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