LONG-TERM HEALTH EFFECTS OF COVID-19:

Musculoskeletal/Fatigue/ Post-Exertional Malaise/Pain

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No conflicts of interest

TOPICS TO BE COVERED

- **Frequency of musculoskeletal *disease* post-COVID**
- **Frequency of persisting *symptoms* post-COVID**
- **Impact of symptoms on *functional capacity***
- **Similarity of post-COVID *symptom profile* to that of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)… and to other post-infection syndromes**
- **Similarity in the emerging underlying *pathophysiology* of Long COVID and ME/CFS**

Post-Acute Sequelae of SARS-CoV-2

VA Health system: ~73,000 people with COVID-19 vs. ~5 million controls without COVID — adjusted for many pertinent covariates, including health care utilization.

Adjusted hazard ratios (HR), all significant, of developing *new* diseases post-COVID over next *4 months*:

- **Myopathies (HR = 5.1)**

Al-Aly Z et al. Nature 2021 Jun 10; 594:259.

Incidence of Persisting Symptoms Following Acute COVID-19

How Common Is "Long COVID?

Hard to answer because studies have been heterogeneous in important ways:

- **Hospitalized vs. non-hospitalized?**
- **Diagnosed by lab test (PCR, Ag, Ab?), "clinical Dx" or self-diagnosis?**
- **Followed as part of a systematic prospective, repeated measures study vs. surveyed at one time point?**
- **Symptoms reported to health professionals as part of study vs. self-reported symptoms from online patient groups**
- **How *severe* the symptoms: functional status?**
- **Followed for how long?**

Symptoms/Function 6 Months Post-COVID

Systematic review of 57 studies involving 250,351 people with COVID-19 (79% hospitalized, 60% with persistent chest imaging abnormalities) followed for 6 months found frequent persistent symptoms:

Symptoms		*Function*	
Fatigue	38%	▼ function	43%
Pain	31%	▼ mobility	20%
Post-exertion malaise	13-50%	▼ exercise tolerance	16%

Groff D, et al. JAMA Network Open 2021;4:e2128568

Post-Exertional Malaise: IOM Case Definition

- **Cardinal symptom of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), according to the National Academy of Medicine**
- ***Definition:*** **A prolonged exacerbation of a patient's baseline symptoms after physical/cognitive/orthostatic exertion or stress. It may be delayed relative to the trigger.**

From: Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Institute of Medicine, 2015.

Cardiopulmonary Exercise Tests in Post-COVID Patients With Exertional Intolerance

	Post-COVID	*Healthy Controls*	*P-value*
Peak VO_2 % Predicted	70±11	131±45	.001
Systemic O_2 extraction	0.5±0.1	0.78±0.1	<.0001
Peak cardiac index	7.8±3.1	8.4±2.3	NS

From: Singh I, et al. Chest 2022;161:54

How Often Does Post-Acute COVID Meet Criteria for ME/CFS?

Following hospitalization for PCR-confirmed COVID-19:

- **47% of cases have persistent fatigue 6 months later**
- **13-25% meet IOM criteria for ME/CFS, 6-9 months later.**

Gonzalez-Hermosillo JA, et al. Brain Sciences 2021;11:760
Mirfazeli FS, et al. Neurolog Sci 2022 doi /10.1007/s10072-021-05786-y

Functional Capacity 9 Months Post-COVID

Population-based cohort study of 51,338 Canadians followed for *9 months* in first year of pandemic. Those with probable or confirmed acute COVID-19 were more likely than those who did not develop COVID-19 to be functionally impaired:

- **Reduced ability to engage in normal household activities (OR 1.89)**
- **Reduced physical activity (OR 1.91)**
- **Difficulty standing from sitting position (OR 2.33)**
- **Similar results for people with suspected COVID-19**

From: Beauchamp MK, et al. JAMA Network Open 5(1):e2146168

Risk Factors for Persistent Symptoms, Post-COVID

- Sickest with *acute* COVID, but….
- Greatest evidence of inflammation/tissue damage with *acute* COVID, but….
- PCR+ vs. PCR-, but….
- Female, but….
- Premorbid asthma/COPD (more likely to develop *non-pulmonary* symptoms post-COVID), but….
- Premorbid history of depression, but….

Post-Infectious Fatigue Syndromes

- Infectious-like illnesses[1-3]
- Epstein-Barr virus[4,6,7]
- Lyme disease[5]
- *Coxiella burnetti*[7]
- Ross River virus[7]
- *Mycoplasma pneumoniae*[8]
- Enteroviruses[9]
- Human herpesvirus-6[10]
- Ebola[11]
- West Nile Virus[12]
- SARS[13]
- Dengue[14]
- Parvovirus[15]
- Giardia[16]
- COVID-19[17]

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Comparison of Pathophysiology: ME/CFS vs. Long COVID - 1

	ME/CFS	LC
Infectious trigger	√ (often)	√√
Dysautonomia/brainstem dysfunction	√√	√√
Autoantibodies, many to neural targets	√√	√√
▼ generation of ATP from O_2, sugar, fats, AAs	√√	√
General hypometabolic state, including in brain	√	√
Redox imbalance (oxidative/nitrosative stress)	√√	√√
Activated & exhausted CD8+ T cells and NK cells	√√	
Gut microbiome dysbiosis: ▲pro-inflammatory species, and ▼anti-inflammatory species	√√	√

Komaroff AL, Lipkin WIL. Trends Mol Med (Cell Press) 2021;27(9):895-906
Paul B, Lemle M, Komaroff AL, Snyder SH. PNAS 2021;118:e2024358118

Comparison of Pathophysiology: ME/CFS vs. Long COVID

	ME/CFS	*LC*
Invasive CPET reveals reduced preload, peak exercise aerobic capacity, O_2 extraction	√	√
Endothelial dysfunction/coagulopathy	√	√√
Reactivation of latent herpesviruses	√	√
Injury and repair in multiple organs		√
Ion channelopathies	√	
Craniocervical instability	√	
Small fiber neuropathy	√	√
Cognitive deficits (esp. attention)	√	√
Neuroinflammation	√	√
Mast cell activation syndrome	√	? √

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Biologic Triggers of Pathology

- Injury and repair in multiple organs ► inflammation
- Persistent reservoirs of virus ► immune response that becomes exhausted
- Viral genome integrated into host genome
- Reactivation of neurotropic pathogens, e.g., herpesviruses
- Mitochondrial dysfunction in T cell subsets
- Chronic inflammation ►oxphos to glycolysis ►deficient ATP generation and a hypometabolic state.
- SARS-CoV-2 ►gut dysbiosis ►chronic inflammation and autoimmunity
- Endothelial dysfunction/coagulopathy
- Dysfunctional brainstem/vagus nerve signaling

Proal AD, VanElzakker MB. Front Microbiol 2021;12:698169
Ramakrishnan RK, et al. Front Immunol 2021;12:686029
Merad M, et al., Science 2022;375:1122–1127

Conclusions

- Musculoskeletal disease and symptoms, fatigue, post-exertional malaise and pain often persist for at least 6 months post-acute COVID-19
- Functional impairment, often attributed to these symptoms, also is common
- These “Long COVID” patients have similar symptoms to people with ME/CFS and other post-infectious syndromes
- They also appear to have similar underlying pathophysiology