Post Covid-19 ME/CFS

Hector Bonilla, MD
Associated Professor IM/ID, Stanford University
Conflicts

• No conflicts of interest
Clinical Criteria for Diagnosis of ME/CFS

• CDC-Fukuda 1994. Chronic fatigue after extensive exclusion work up of other illness (> 6 months)
• Canadian Consensus 2010. The outline is Post Exertional Malaise (PEM) and pain (> 6 months)
• Institute of Medicine IOM 2015

Annals of Internal Medicine, December 15, 1994,
Canadian Consensus Criteria May 15, 2012
Proposed Diagnostic Criteria for ME/CFS

Diagnosis requires that the patient have the following three symptoms:

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities, that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, and
2. Post-exertional malaise,* and
3. Unrefreshing sleep*

At least one of the two following manifestations is also required:

1. Cognitive impairment* or
2. Orthostatic intolerance

* Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.

For more information, visit www.iom.edu/MECFS
Burden of ME/CFS

- Affects 836,000 – 2.5 million in the US
- Predominant woman
- Age of onset 33 YO (range 10-77 YO)
- The symptoms persist for years
- Economical impact to the society over $18-24 billion

Jason Arch Int Med, 1990
Reynolds, Cost Effectiveness and resources allocation 2004
Jason, Dynamic Medicine, 2008
Long COVID Definition

- **CDC**
  - >28 days since first symptoms

- **NICE**
  - Symptomatic COVID-19 (from 4 to 12 weeks)
  - Post-COVID-19 syndrome (≥12 weeks)

- **WHO**
  - 3 months from onset of COVID-19 symptoms and that last > 2 months and cannot be explained by an alternative diagnosis

- **UK Office for National Statistics**, an estimated 945 000 people had self-reported long COVID on July 4, 2021. Prevalence 1.5% of the population

Delphi consensus, 6 October 2021
39 year old healthy female, working as an executive assistant, and physical very active (ride bike by several miles). PMH anemia and low iron levels treated by her PCP with iron. May 2017 she developed a papular vesicular rash in the right lumbar area following an L2/L3 dermatome distribution.
Three weeks later she had sore throat, congestion, worsening fatigue, brain fog, malaise, pain in her extremities enlarged tonsils with exudate, strep test (-). Monospot (+), EBV, VCA IgG, and IgM positive and ALT/ST 10-20 x normal values. She was treated by her PCP with Valacyclovir.
Case 1

• The patient had a resolution of the tonsillitis and hepatitis
• However, the patient has persistent incapacitating fatigue, cognitive dysfunction (memory, concentration, and information processing), and unrefreshing sleep
• These symptoms interfere with her personal, social, and professional life
• Her fatigue is exacerbated by physical activity, stress, or overstimulation
• She also experiences post exertional malaise that includes worsening fatigue, brain fog, sore throat, myalgias, and neuropathic pain in her extremities. These symptoms were not substantially alleviated by rest
• Six month later she was evaluated at the Stanford ME/ CFS clinic that confirmed the clinical diagnosis of chronic fatigue syndrome.
37 yo female in December 2017 had a vacation trip to Cabo San Lucas, presented 8 days after her trip with 4 days of severe watery diarrhea, myalgias, fatigue, loss of appetite, low-grade fever, and a diffuse maculopapular pruritic rash. CBC revealed leukopenia (WBC 1800) and neutropenia (absolute neutrophils 0.92). PCR blood testing for Zika virus was positive. CDC in Fort Collins an arbovirus positive IgM Zika IgM and Dengue serotype 1
Case 2

• The patient over next two years post infections, continued to experience waxing and waning fatigue, post-exertional malaise and slowed cognition for several months. As a person who could previously hike 20 miles in a day, she could now walk only 2 miles, 1-2 times per week, or just 50 feet

• During her worst symptom flares diffuse joint pains and reported a persistent frontal headache and “brain fog” with any overexertion and seen several times in ER

• She was evaluated in the ME/CFS clinic and Dx with ME/CFS
Stanford PACS

• 109 Dx PACS
• Criteria Covid clinical symptoms, and Covid-19 test (+): PCR, Ag or antibodies before vaccination
• Follow 29 symptoms grade severity Likert scale (1→5)
• Risk factors for severity of illness
• Functional Status (I→V)
Stanford ME/CFS

- More than 180 days (six months) of infection
- Fatigue Likert scale >4
- Functional status >III
- Institute of Medicine criteria:
  - Severe and incapacitating fatigue
  - Unrefreshing sleep
  - PEM
  - Other: Orthostatic intolerance or “brain fog”
### Post Covid-19 Stanford Cohort

104 patient follow at the PACS clinic

10 Excluded

94 patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>POST-COVID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean-range)</td>
<td>46.67 (20-77)</td>
</tr>
<tr>
<td>Days post-Covid (mean-range)</td>
<td>280 (42-591)</td>
</tr>
<tr>
<td>SEX N (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>51 (54%)</td>
</tr>
<tr>
<td>Male</td>
<td>43 (46%)</td>
</tr>
<tr>
<td>RACE N (%)</td>
<td></td>
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<tr>
<td>White</td>
<td>57 (61%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (4%)</td>
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<tr>
<td>Asian</td>
<td>14 (15%)</td>
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<tr>
<td>No report</td>
<td>8 (9%)</td>
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<tr>
<td>DIAGNOSTIC N (%)</td>
<td></td>
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<tr>
<td>Covid Dx PCR</td>
<td>80 (86%)</td>
</tr>
<tr>
<td>Covid Dx Antigen</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Covid Dx Antibodies</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>TREATMENT N (%)</td>
<td></td>
</tr>
<tr>
<td>Treatment Ambulatory</td>
<td>75 (80%)</td>
</tr>
<tr>
<td>Treatment Hospital</td>
<td>17 (18%)</td>
</tr>
<tr>
<td>Treatment ICU</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>COMORBIDITY N (%)</td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>53 (56%)</td>
</tr>
<tr>
<td>1 comorbid condition</td>
<td>28 (30%)</td>
</tr>
<tr>
<td>2 comorbid conditions</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>3 or more comorbid conditions</td>
<td>6 (7%)</td>
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<tr>
<td>Severity Illness (Infection) N (%)</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>37 (39%)</td>
</tr>
<tr>
<td>IV</td>
<td>15 (16%)</td>
</tr>
<tr>
<td>III</td>
<td>31 (33%)</td>
</tr>
<tr>
<td>II</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>No Data</td>
<td>7 (7%)</td>
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<tr>
<td>Severity Illness (Initial Assessment) N (%)</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>IV</td>
<td>24 (26%)</td>
</tr>
<tr>
<td>III</td>
<td>48 (52%)</td>
</tr>
<tr>
<td>II</td>
<td>13 (14%)</td>
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</tbody>
</table>
ME/CFS in Post Covid Population

94 patients:
>180 days (70 patients)
- Clinical state (III, IV, and V)
- IOM Criteria

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ME/CFS STUDY POPULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ME/CFS</td>
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<tr>
<td>Age (mean-range)</td>
<td>47.51</td>
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<tr>
<td>Days post-Covid (mean-range)</td>
<td>330 (591-183)</td>
</tr>
<tr>
<td>SEX N (%)</td>
<td></td>
</tr>
<tr>
<td>Female/male N (%)</td>
<td>24 (62%)</td>
</tr>
<tr>
<td>RACE N (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>28 (71%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Black</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>No report</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>TREATMENT N (%)</td>
<td></td>
</tr>
<tr>
<td>Treatment Ambulatory</td>
<td>33 (85%)</td>
</tr>
<tr>
<td>Treatment Hospital</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Treatment ICU</td>
<td>0</td>
</tr>
<tr>
<td>COMORBIDITY N (%)</td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>20 (51%)</td>
</tr>
<tr>
<td>1 comorbid condition</td>
<td>11 (28%)</td>
</tr>
<tr>
<td>2 comorbid conditions</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>3 or more comorbid conditions</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>BMI &gt;35</td>
<td>7</td>
</tr>
<tr>
<td>IOM Criteria</td>
<td></td>
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<tr>
<td>5/5</td>
<td>29 (74%)</td>
</tr>
<tr>
<td>4/5</td>
<td>10 (26%)</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
</tr>
</tbody>
</table>

ME/CFS VS No ME/CFS

31 (44%)
39/56%
Cytokines ME/CFS- Immunology

• Landi, 34 cytokines in 100 ME/CFS pts vs 79 controls. Significant
  ➢ IL-16, IL-7, and VEGF-A (Low levels)
  ➢ CX3CL1, MIG and CXCL9 (Low levels)
  ➢ CCL24 (Increase)

• Montoya, 51 cytokines in 192 ME/CFS pts vs. 392 controls. Significantly high levels in 17/51
  ➢ Resistin (Low levels)
  ➢ TGF-β was elevated

Landi A., Cytokine, 2016
Montoya, PNAS, 2017
NK Cell Function ME/CFS

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Control</th>
<th>ME/CFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number cases</td>
<td>234</td>
<td>102</td>
<td>132</td>
</tr>
<tr>
<td>Age (mean (SD))</td>
<td>44.39 (14.75)</td>
<td>39.79 (12.81)</td>
<td>47.17 (15.19)</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>160 (68.4)</td>
<td>71 (69.6)</td>
<td>89 (67.4)</td>
</tr>
<tr>
<td>Male</td>
<td>73 (31.2)</td>
<td>30 (29.4)</td>
<td>43 (32.6)</td>
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<tr>
<td>missing</td>
<td>1 (0.4)</td>
<td>1 (1.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
Example of a control brain on top and a chronic fatigue syndrome brain on bottom. The ventricles are larger in the chronic fatigue syndrome patient, and there is less white matter. Abnormal microstructure is present on one side in the white matter in chronic fatigue syndrome.
Translocator protein 18 kDa (TSPO): imaging biomarker of glial activation

- Primarily located in outer mitochondrial membrane
- Present in low levels in healthy CNS
- Over-expressed in neurodegenerative and inflammatory diseases
- Marker of glial activation
- Inflammatory responses
- Oxidative stress
- Mitochondrial homeostasis

Courtesy of Michelle James
[¹¹C]DPA-713-PET: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) (30-60 min summed images)

**ME/CFS** Female, Age 39

**Healthy Control** Female, Age 37
TSPO-PET: pseudo-reference region identification and time activity curves

Cerebral White matter

Cerebellum White matter

Cerebellum Cortex

Mackenzie Carlson

MIPS Molecular Imaging Program at Stanford

James & Zeineh Labs, Unpublished Data
Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An $^{11}$C-(R)-PK11195 PET Study

Yasuhiro Nakatomi$^{1,2}$, Kei Mizuno$^{2-4}$, Akira Ichii$^{5,3}$, Yasuhiro Wada$^{2,3}$, Masaaki Tanaka$^{5,3}$, Shusaku Tazawa$^{2,3}$, Kayo Onoe$^{3}$, Sanae Fukuda$^{3}$, Joji Kawabe$^{3}$, Kazuhiro Takahashi$^{2,3}$, Yusky Kataoka$^{2,3}$, Susumu Shiotani$^{2}$, Kouzi Yamaguti$^{3}$, Masaaki Inaba$^{1}$, Hirohiko Kuratsune$^{3,6,7}$, and Yasuyoshi Watanabe$^{2,3}$

$^{1}$Department of Metabolism, Endocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan; $^{2}$RIKEN Center for Life Science Technologies, Hyogo, Japan; $^{3}$Department of Physiology, Osaka City University Graduate School of Medicine, Osaka, Japan; $^{4}$Department of Medical Science on Fatigue, Osaka City University Graduate School of Medicine, Osaka, Japan; $^{5}$Department of Nuclear Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan; $^{6}$Department of Health Science, Kansai University of Welfare Sciences, Osaka, Japan; and $^{7}$Graduate School of Agricultural and Life Sciences, University of Tokyo, Tokyo, Japan.

• The **midbrain** motor movement, particularly movements of the eye, and in auditory and visual processing
• The **Pons** relay messages from the cortex and the cerebellum. It also plays a role in sleep and dreaming
• The **thalamus** sensory information auditory, visual, tactile, and gustatory signals. Directs the sensory information to the different parts and lobes of the cortex
• The **cingulate** gyrus processing emotions and behavior regulation. It helps to regulate autonomic motor function
• The **Amygdala** Responsible for the response and memory of emotions, especially fear
• The **hippocampus** is part of the **limbic system**, and short-term memory to long-term memory, and in spatial memory that enables navigation

ME/CFS: whole-brain magnetic resonance spectroscopy

- 15 females ME/CFS
- 15 matched healthy control
- Magnetic Resonance Spectroscopy
- CHO, MI, LAC and NAA in 47 regions
- Relationship between:
  - metabolite ratios
  - brain temperature
  - fatigue in ME/CFS

- Elevations of CHO, LAC, MI, and temperature in ME/CFS group, as well as lower levels of the neuronal marker NAA
- Indicators of microglial cell activation and inflammation

Mueller C, Brain Imaging Behav. 2020
Cellular bioenergetics is impaired in patients with chronic fatigue syndrome

Cara Tomas, Audrey Brown, Victoria Strassheim, Joanna Elson, Julia Newton, Philip Manning

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total participants</td>
<td>35</td>
<td>52</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>36.6±12.0</td>
<td>42.8±13.7</td>
</tr>
<tr>
<td>Female/male ratio</td>
<td>27/8</td>
<td>44/8</td>
</tr>
</tbody>
</table>

A. Basal respiration
B. ATP production
C. Proton leak
D. Maximal respiration
E. Reserve capacity
F. Non-mitochondrial respiration
G. Coupling efficiency
1,484 in hospitalized patients MSHS NYC with acute Covid-19 infection, IL-6, IL-8 and TNF-α levels predictors of patient survival (P < 0.0001, P = 0.0205 and P = 0.0140, respectively)

Del Valle DM, Nat Med, 2020
Witkowski M, Nature, 2021
Persistent “Inflammation”

101 Patients Covid-19 (+)
- 38 mild
- 34 moderate
- 29 severe
24 Healthy Controls
180 days post infection

Xiang Ong SW. Open forum Infect Dis. 2021

BDNF, brain-derived neurotrophic factor
HGF, hepatocyte growth factor
IL, interleukin; MIP, macrophage inflammatory protein
SCF, stem cell factor
VEGF, vascular endothelial growth factor.
Neuroinflammation COVID-19

**Neuroinflammation**

8 pts COVID-19/ 14 control (1 pt with influenza)
- Perivascular macrophages
- T cell
- Microglial cells

- Strongest effects in astrocytes and other glia
- Upregulation of gene *IFITM3* (choroid and glia cells) consistent with SARS-CoV-2 infection
- qPCR SARS-CoV-2 negative
- Poss. earlier neuro-invasion that subsequently cleared

Yang A. Nature, 2021
Mitochondrial metabolic manipulation by SARS-CoV-2 in peripheral blood mononuclear cells of patients with COVID-19

9 Healthy controls
7 Covid-19
7 Pulmonary infection

A. Basal respiration
B. ATP production
C. Maximal respiration
D. Reserve capacity
E. Non-mitochondrial respiration
F. Proton leak
Conclusions

• Similarities in the clinical presentations of both ME/CFS and ME/CFS Post-Covid
• ME/CFS Post-Covid more common in white Females, Healthy individual and mild to moderated Covid-19 infection
• Both ME/CFS and ME/CFS Post-Covid are characterized in cytokines abnormalities
• NK cells low function present in ME/CFS, and acute covid with poor clinical outcome
• Evidence of neuro-inflammation was demonstrated in both ME/CFS and ME/CFS Post-Covid
• Those findings need to validate and a multicentric and larger cohort
ME/CFS Treatment
VS
ME/CFS-post Covid
PACS Multi-Disciplinary Clinical Team/Network

Dept of Medicine
Dr. Hector Bonilla* (Infectious Diseases)
Dr. Lauren Eggert (Pulmonary, Allergy & Critical Care)
Dr. Linda Geng* (Internal Medicine)
Dr. Houssam Halawi (Gastroenterology)
Dr. Audra Horomanski (Rheumatology/Immunology)
Dr. Robert Shafer* (Infectious Disease)
Dr. Husham Sharifi (Pulmonary, Allergy & Critical Care)
Dr. Aruna Subramanian (Infectious Diseases)
Dr. Phillip Yang (Cardiology)

Dept of Neurology
Dr. Mitchell Miglis (Neuro: Autonomic & Sleep)

Dept of Psychiatry
Dr. Jacob Ballon (Psychiatry: Psychotic disorders)
Dr. Agnieszka Kalinowski (Psychiatry)
Dr. Norah Simpson (Psychology / Insomnia, CBTi)
Dr. Oliver Sum-Ping (Sleep Medicine)

Dept of Otolaryngology
Dr. Zara Patel (ENT: Skull Base, Rhinology)

Dept of Radiology
Dr. Michael Zeineh
Dr. Michelle James

*hub/portal clinic
Thank You!