Post Covid-19 ME/CFS

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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

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* 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**

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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

- <u>CDC</u>
  - ✓>28 days since first symptoms
- <u>NICE</u>
  - ✓Symptomatic COVID-19 (from 4 to 12 weeks)
  - ✓Post-COVID-19 syndrome (≥12 weeks)
- <u>WHO</u>
  - ✓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

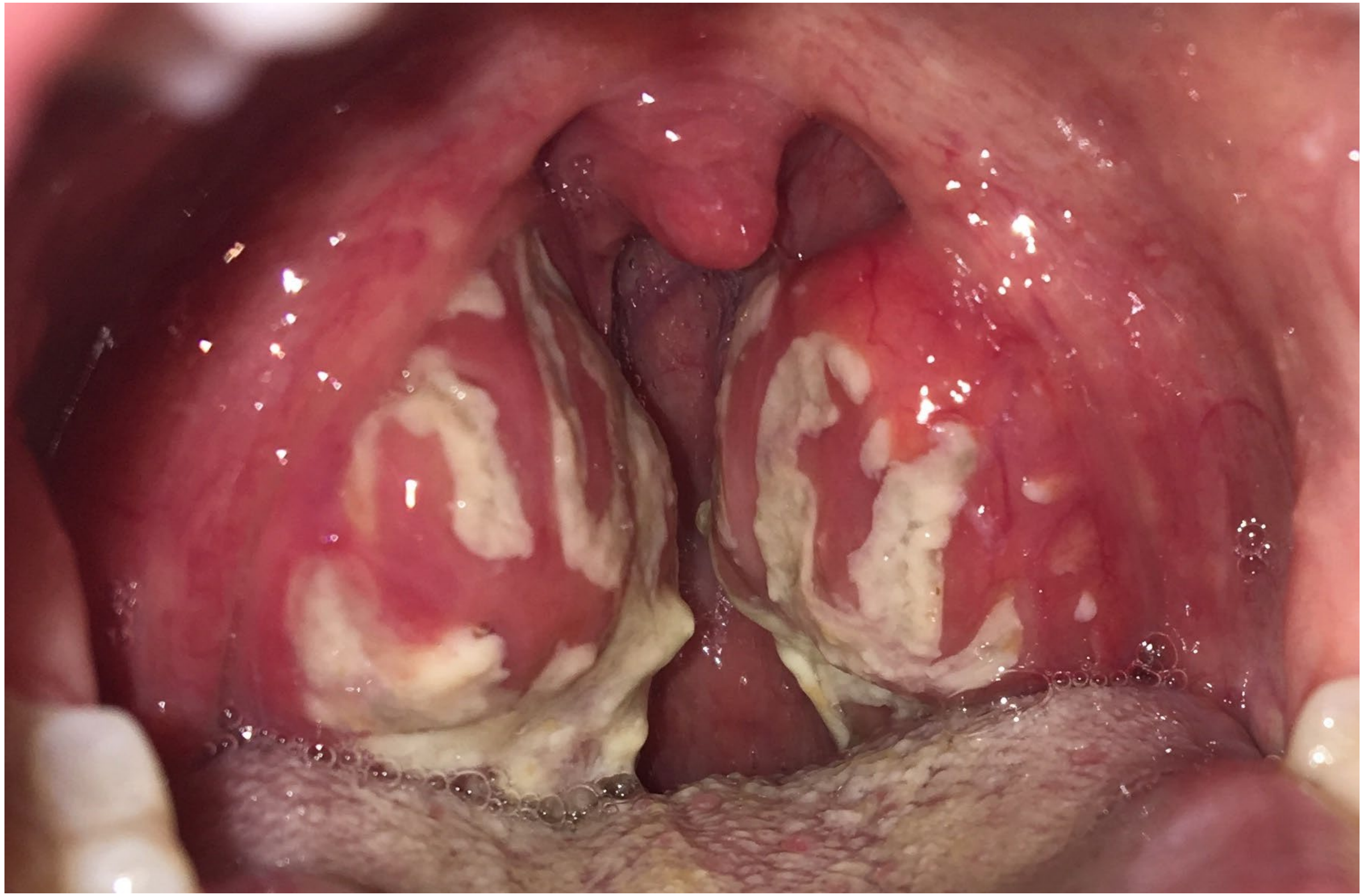
Office for National Statistics

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

World Health Organization
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

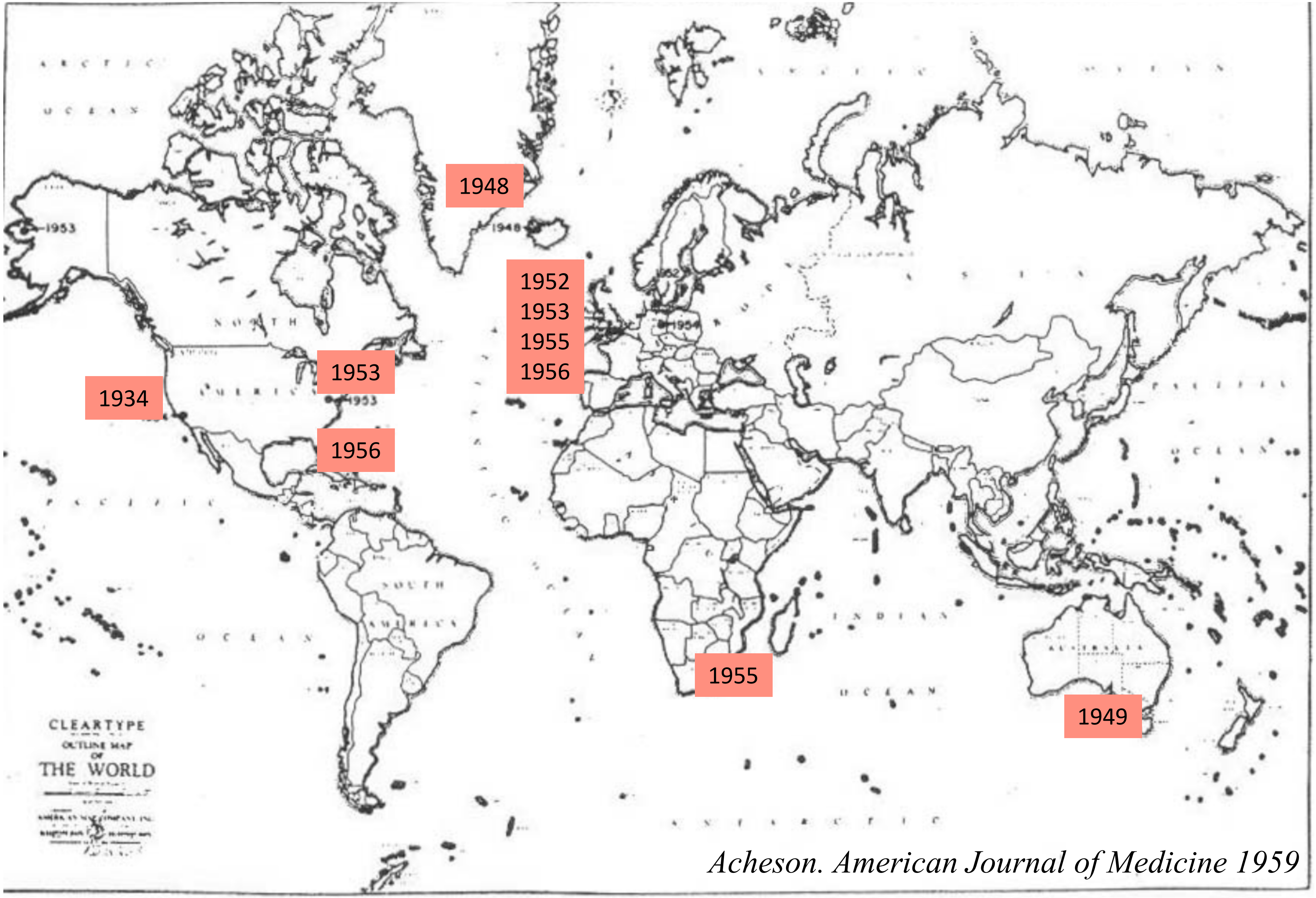
Case 1

- 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



Geographical Distribution of Outbreaks

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

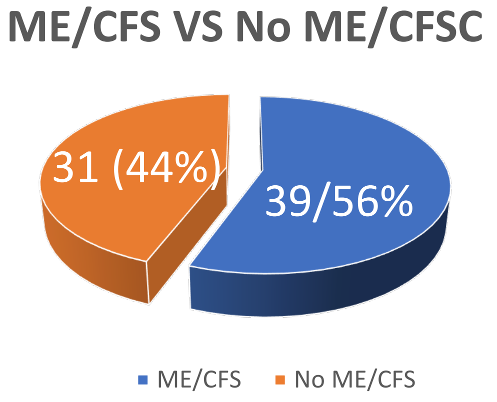
104 patient follow at the PACS clinic → 10 Excluded → 94 patients

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

ME/CFS in Post Covid Population

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

Characteristics	ME/CFS STUDY POPULATION	
	ME/CFS	No ME/CFS
Age (mean-range)	47.51	46.03
Days post-Covid (mean-range)	330 (591-183)	309 (31-522)
SEX N (%)		
Female/male N (%)	24 (62%)/15 (38%)	18 (58%)/13 (42%)
RACE N (%)		
White	28 (71%)	22 (71%)
Hispanic	4 (10%)	2 (6%)
Black	0	1 (3%)
Asian	3 (8%)	3 (10%)
No report	4 (10%)	3 (10%)
TREATMENT N (%)		
Treatment Ambulatory	33 (85%)	25 (81%)
Treatment Hospital	6 (15%)	6 (19%)
Treatment ICU	0	1
COMORBIDITY N (%)		
Healthy	20 (51%)	20 (65%)
1 comorbid condition	11 (28%)	8 (26%)
2 comorbid conditions	5 (13%)	1 (3%)
3 or more comorbid conditions	3 (8%)	2 (6%)
BMI >35	7	4
IOM Criteria		
5/5	29 (74%)	-
4/5	10 (26%)	-
Total	39	31

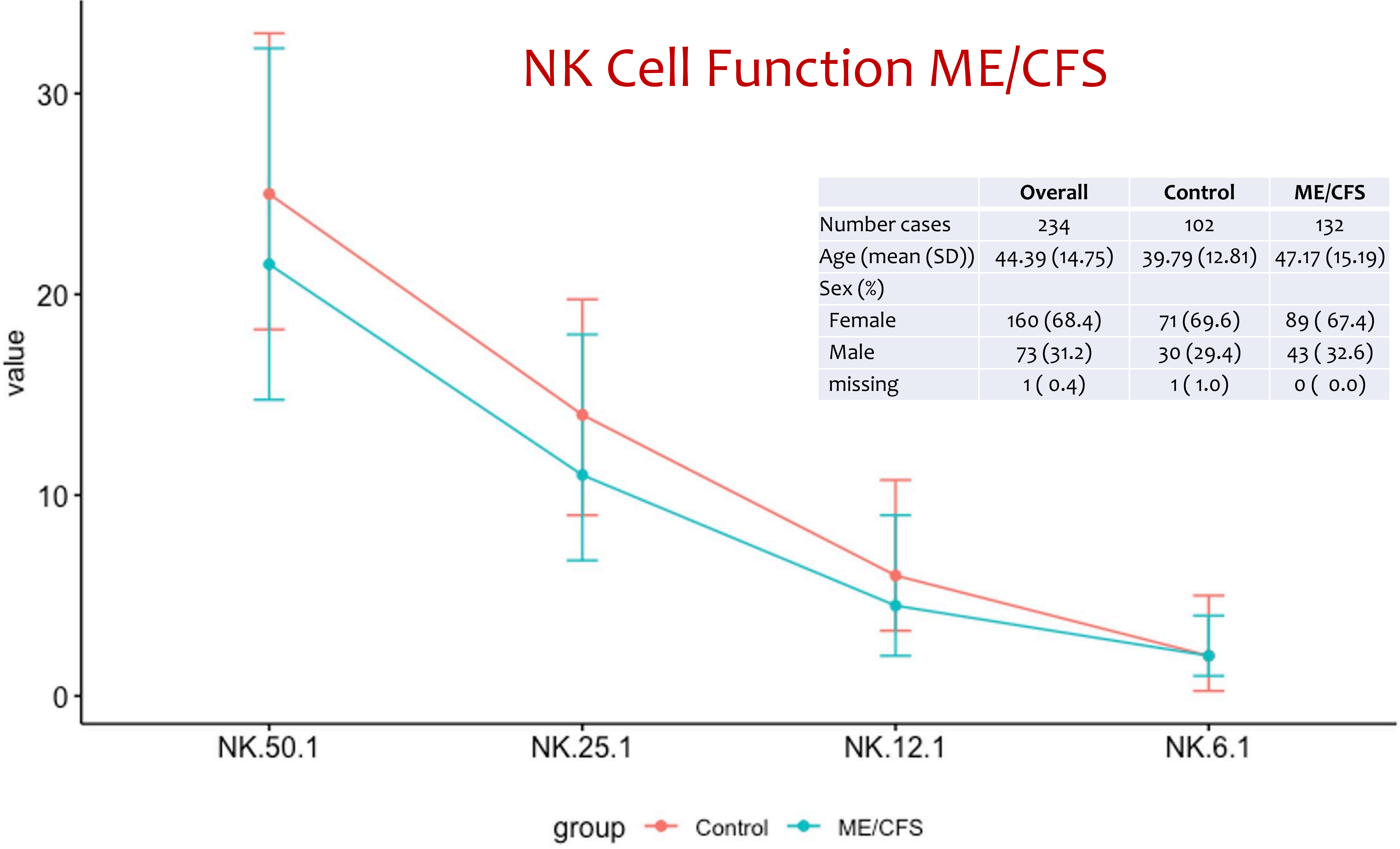


Cytokines ME/CFS- Immunology

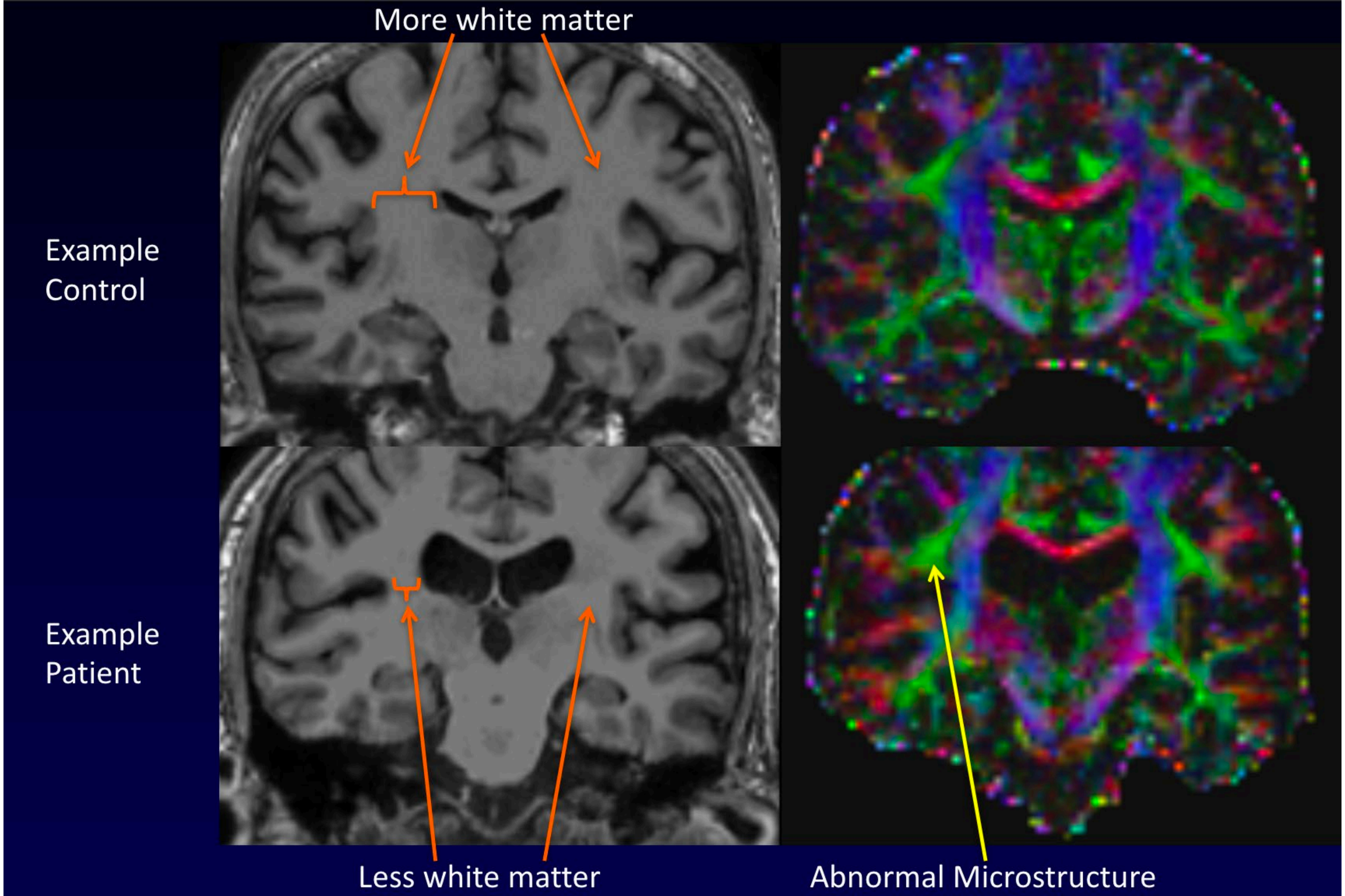
- Landi, 34 cytokines in 100 ME/CFS pts vs 79 controls. Significant
  - IL-16, IL-7, and VEGF-A (Low levels)
  - CX3CL1, MIG and CXCL9 (Low levels)
  - CCL24 (Increase)
- Montoya, 51 cytokines in 192 ME/CFS pts vs. 392 controls. Significantly high levels in 17/51
  - Resistin (Low levels)
  - TGF-β was elevated

Landi A., Cytokine, 2016
Montoya, PNAS, 2017

NK Cell Function ME/CFS



	Overall	Control	ME/CFS
Number cases	234	102	132
Age (mean (SD))	44.39 (14.75)	39.79 (12.81)	47.17 (15.19)
Sex (%)			
Female	160 (68.4)	71 (69.6)	89 (67.4)
Male	73 (31.2)	30 (29.4)	43 (32.6)
missing	1 (0.4)	1 (1.0)	0 (0.0)

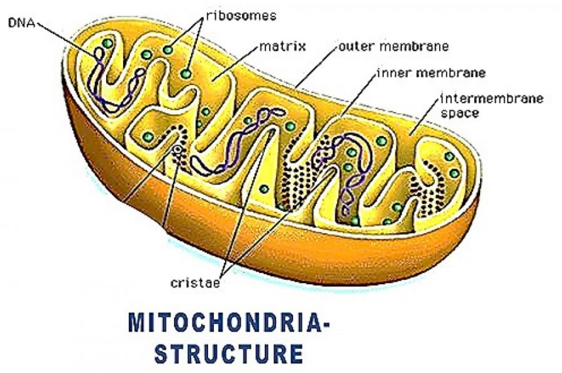


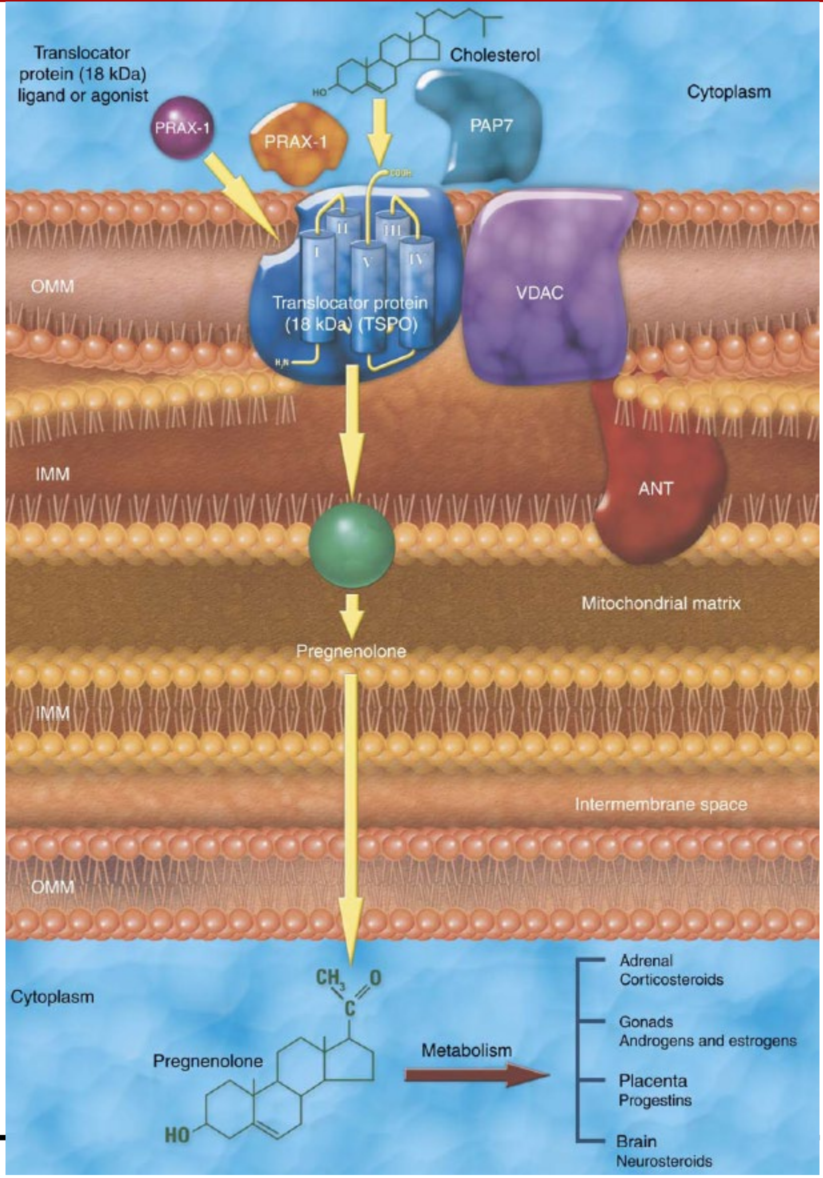
Example of a control brain on top and a chronic fatigue syndrome brain on bottom. The ventricles are larger in the chronic fatigue syndrome patient, and there is less white matter. Abnormal microstructure is present on one side in the white matter in chronic fatigue syndrome.

http://med.stanford.edu/zeinehlab.html

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





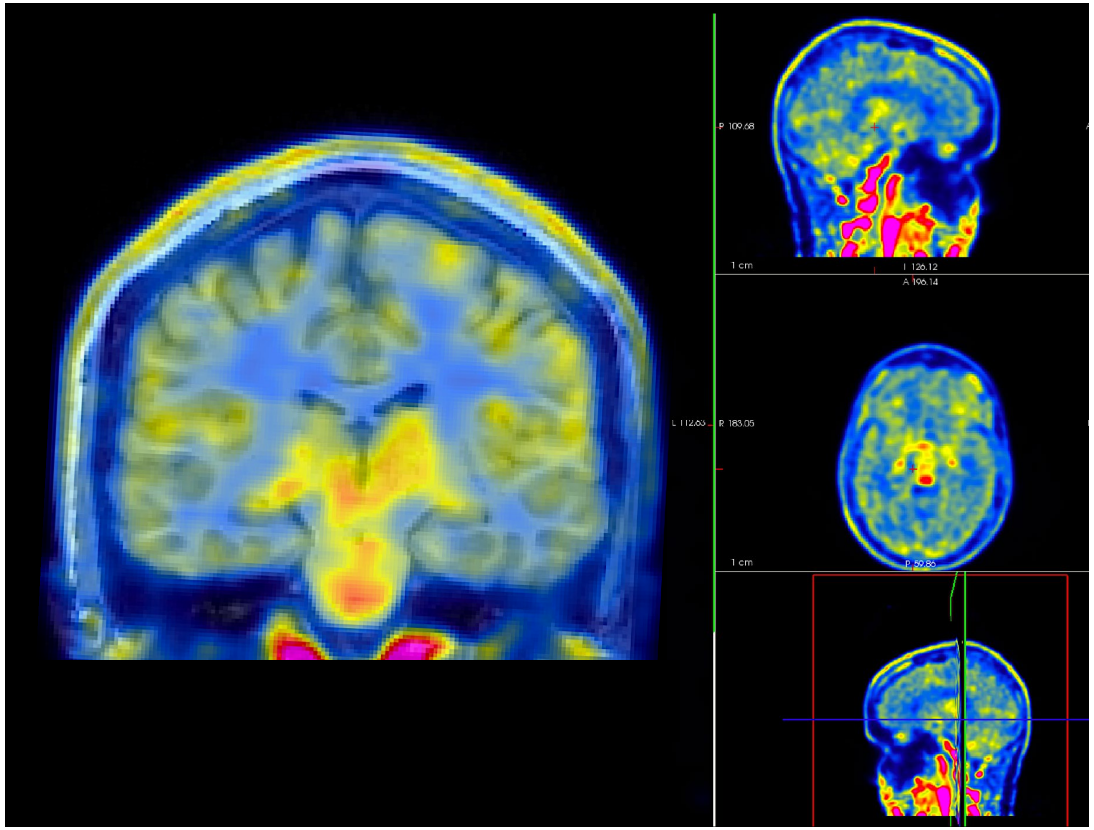
Courtesy of Michelle James

MIPS Molecular Imaging Program at Stanford

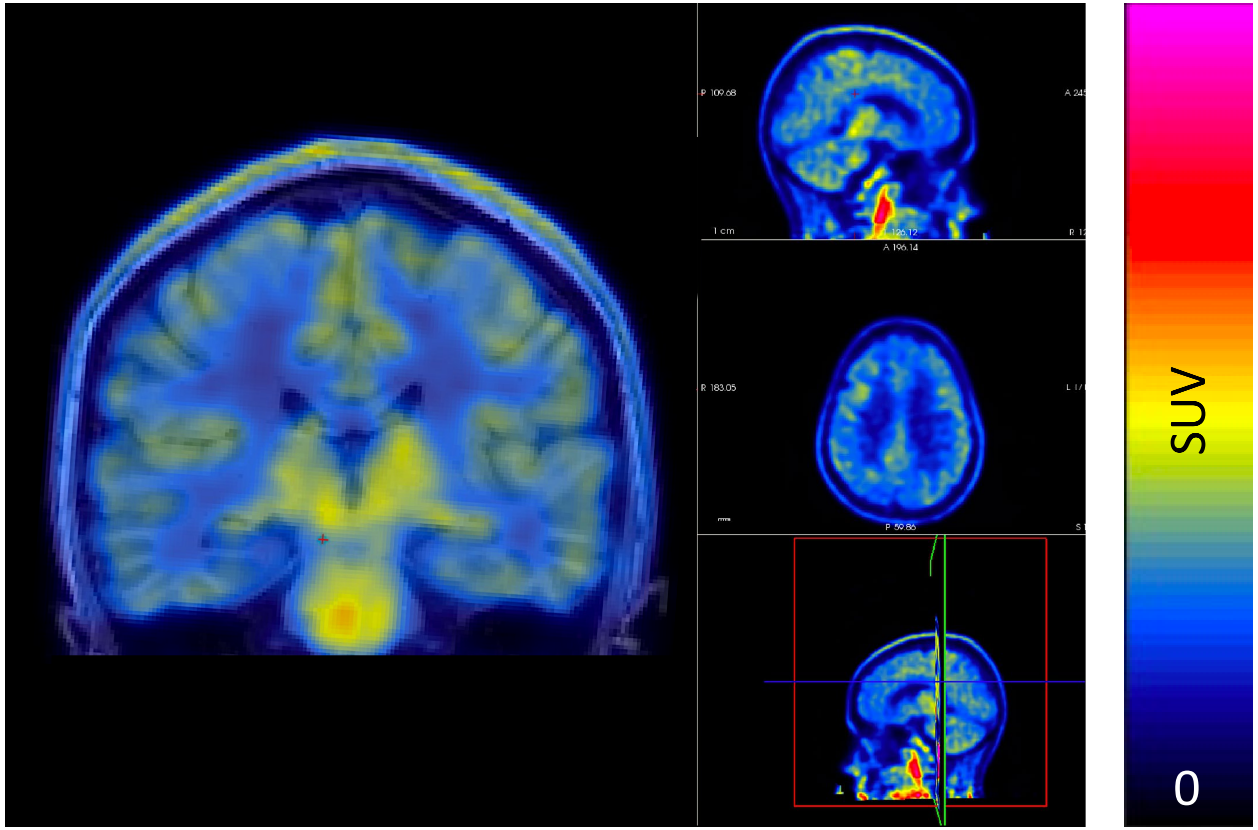
[11]C]DPA-713-PET: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

(30-60 min summed images)

ME/CFS Female, Age 39



Healthy Control Female, Age 37



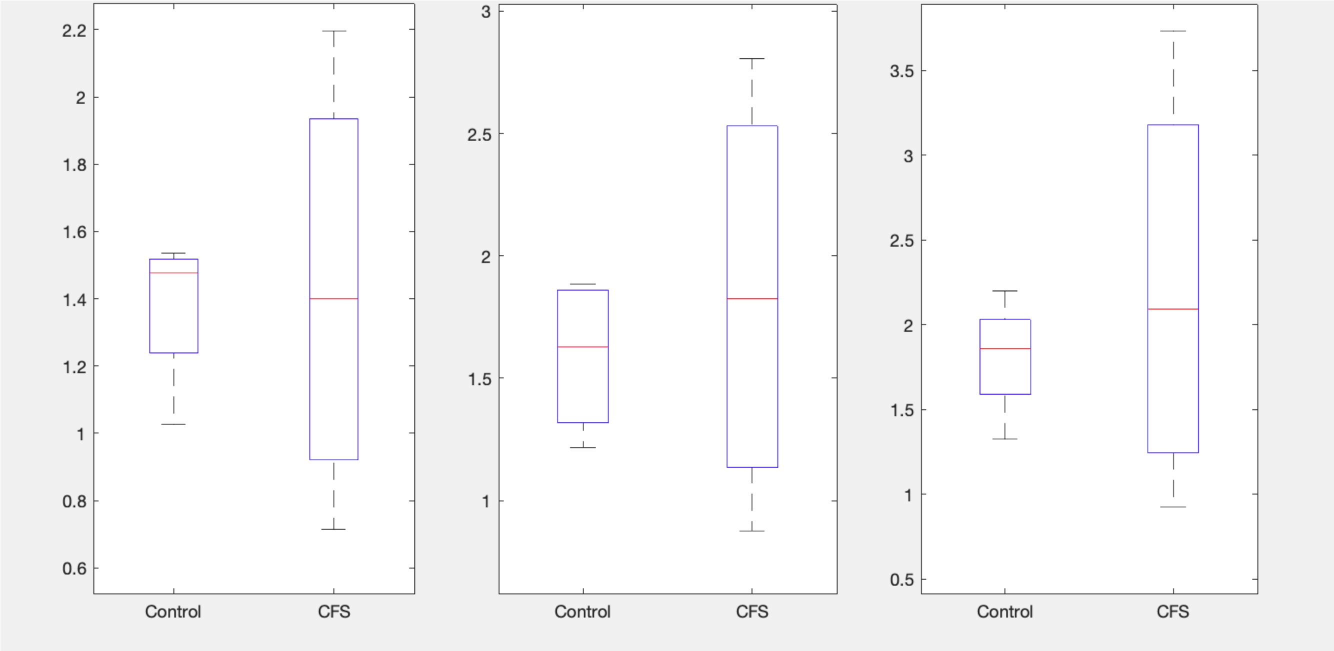
MIPS
Molecular Imaging Program at Stanford

James & Zeineh Labs, Unpublished Data

TSPO-PET: pseudo-reference region identification and time activity curves

Mackenzie Carlson

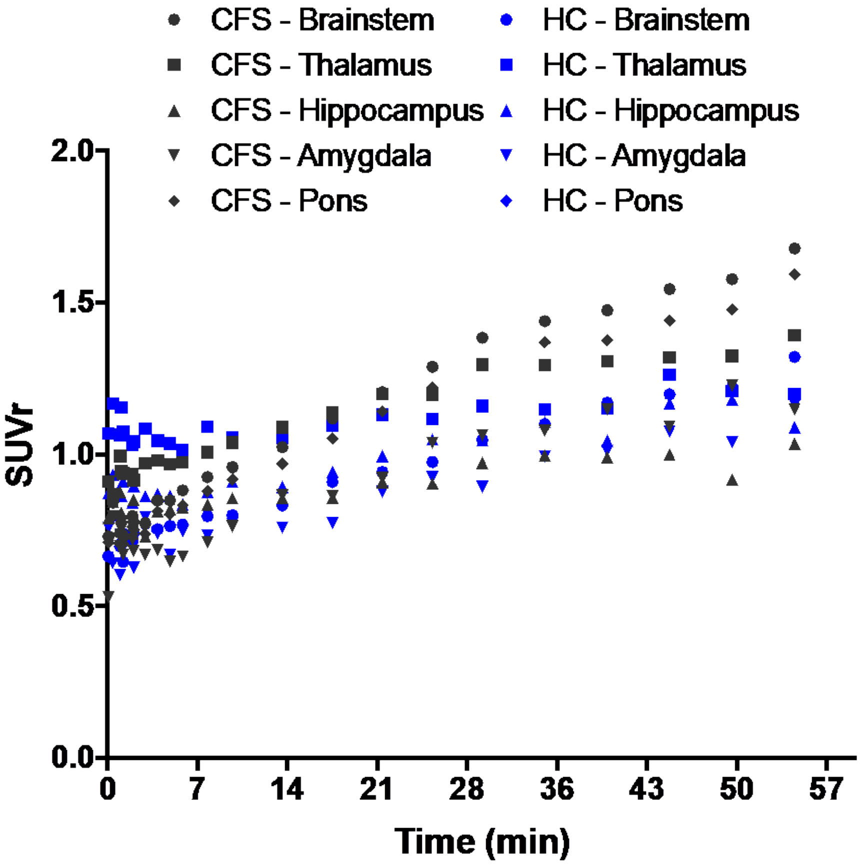
Cerebral White matter | Cerebellum White matter | Cerebellum Cortex



p = 0.8905

p = 0.6157

p = 0.5552



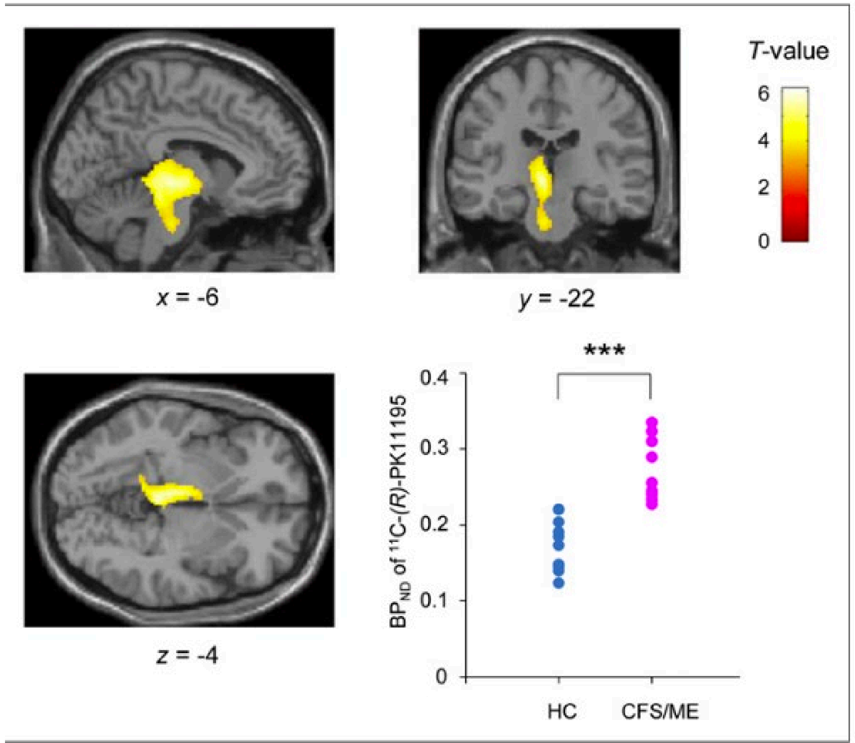
MIPS Molecular Imaging Program at Stanford

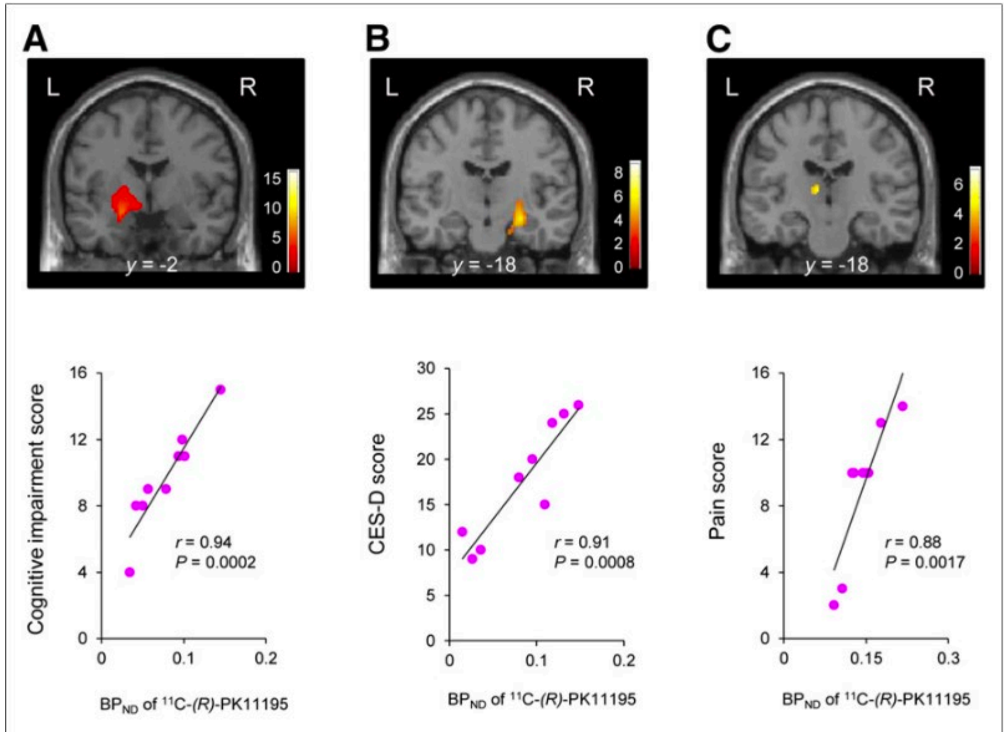
James & Zeineh Labs, Unpublished Data

Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An ^{11}C-(R)-PK11195 PET Study

Yasuhito Nakatomi[1,2], Kei Mizuno[2–4], Akira Ishii[2,3], Yasuhiro Wada[2,3], Masaaki Tanaka[2,3], Shusaku Tazawa[2,3], Kayo Onoe[2], Sanae Fukuda[2,3], Joji Kawabe[5], Kazuhiro Takahashi[2,3], Yosky Kataoka[2,3], Susumu Shiomi[5], 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





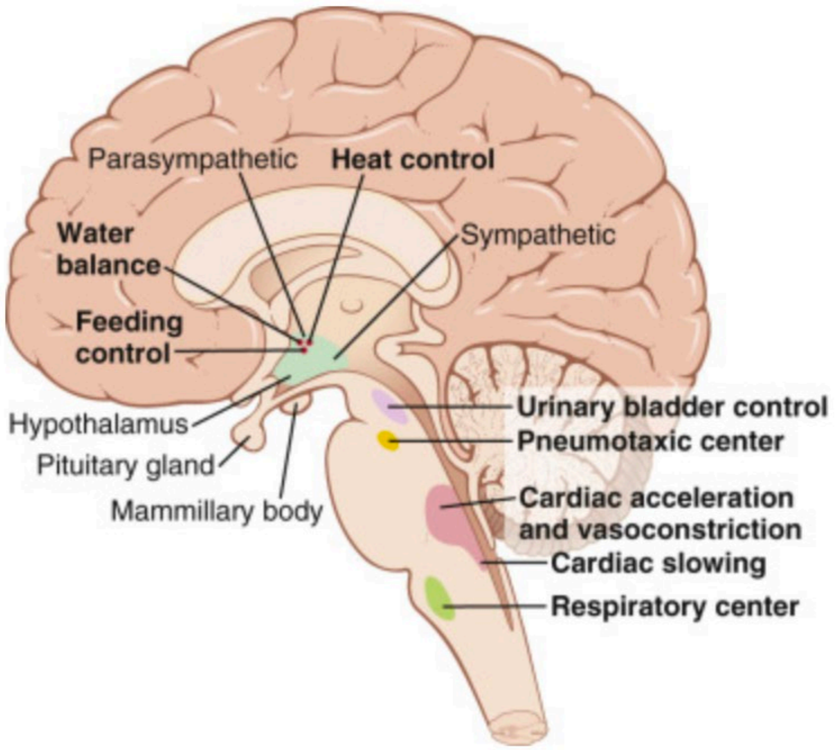
Nakatomi Y, J. Nucl Med 2014

Regional ^{11}C-(R)-PK11195 BP_{ND} in CFS/ME Patients and Healthy Controls

Region	CFS/ME	Healthy control	*P*	Increase (%)
Midbrain	0.181 ± 0.027	0.123 ± 0.024	0.0001	47
Pons	0.155 ± 0.030	0.107 ± 0.028	0.0021	45
Thalamus	0.097 ± 0.021	0.058 ± 0.023	0.0013	66
Cingulate	0.010 ± 0.008	0.003 ± 0.003	0.0353	199
Amygdala	0.057 ± 0.031	0.031 ± 0.025	0.0586	85
Hippocampus	0.053 ± 0.023	0.029 ± 0.017	0.0212	81

Data are mean ± SD. Student *t* tests or Fisher exact test was conducted.

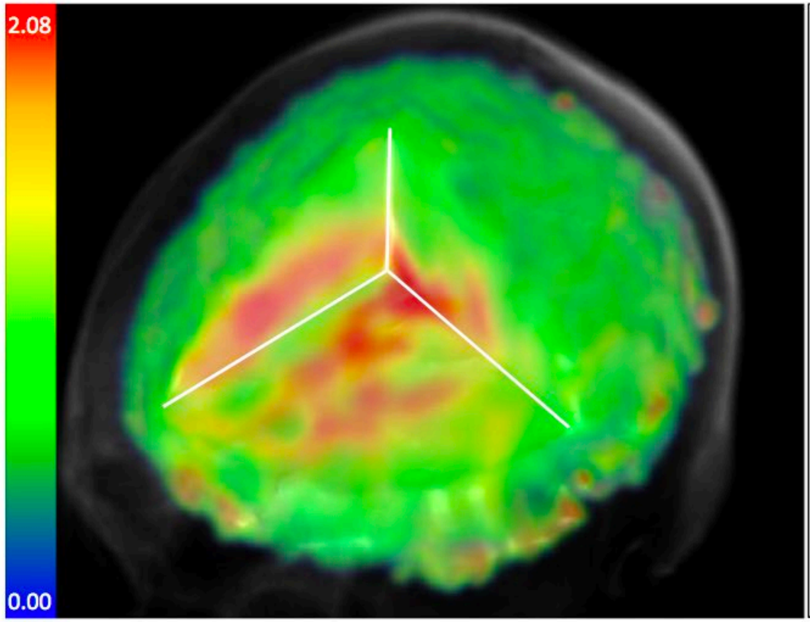
- The **midbrain** motor movement, particularly movements of the eye, and in auditory and visual processing
- The **Pons** relay messages from the cortex and the cerebellum. It also plays a role in sleep and dreaming
- The **thalamus** sensory information auditory, visual, tactile, and gustatory signals. 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

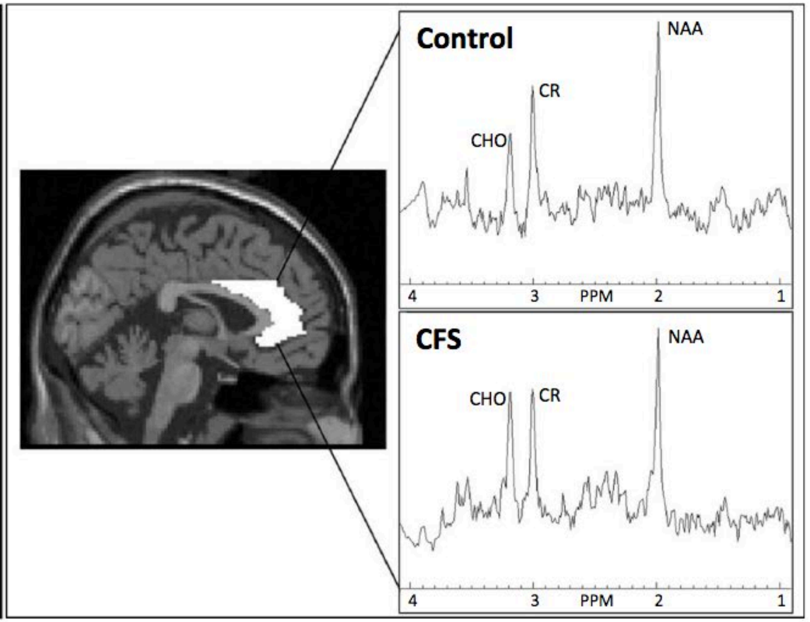


Nakatomi Y, J. Nucl Med 2014

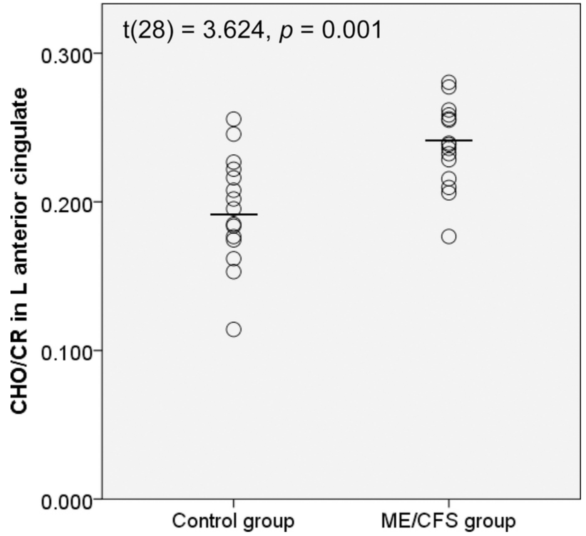
ME/CFS: whole-brain magnetic resonance spectroscopy

- -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

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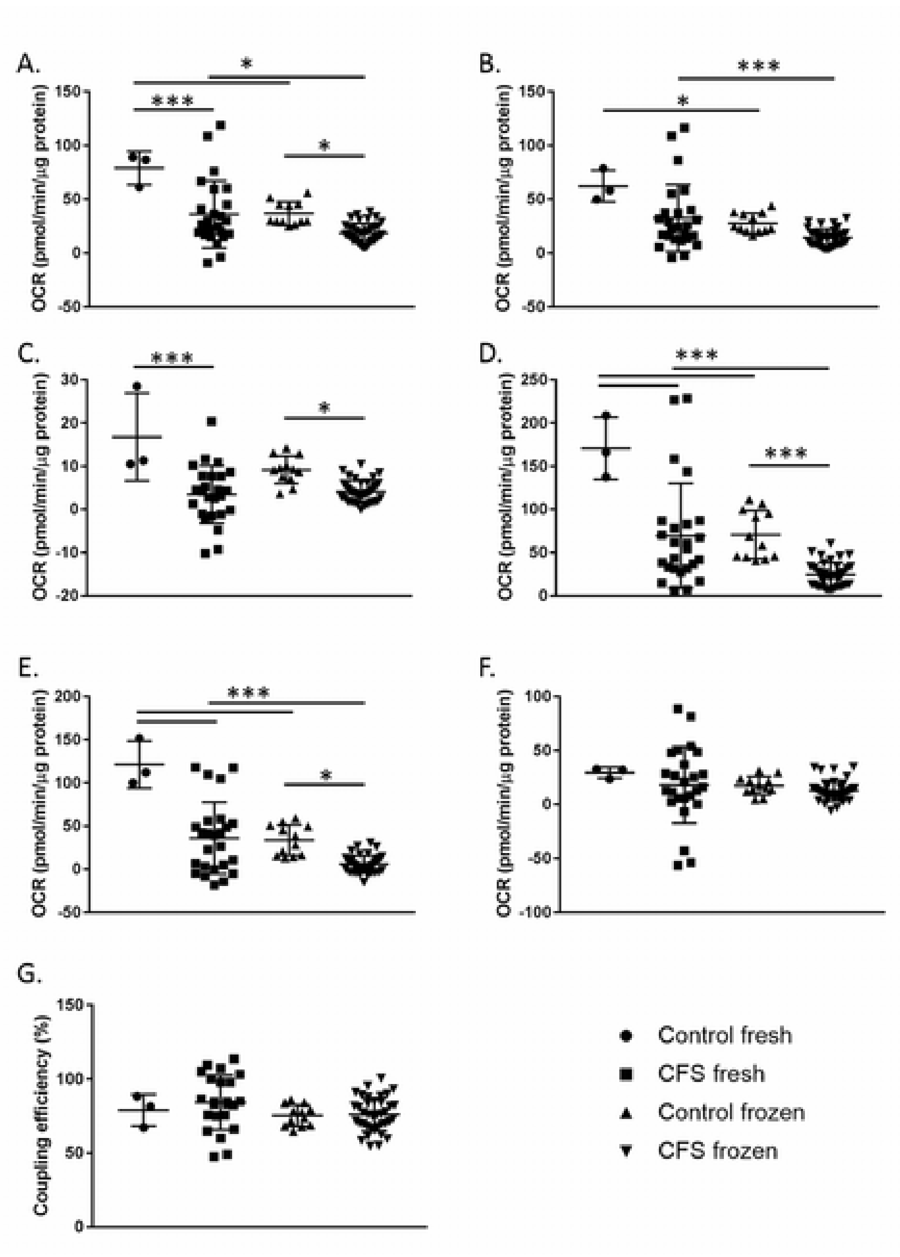
Cellular bioenergetics is impaired in patients with chronic fatigue syndrome

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

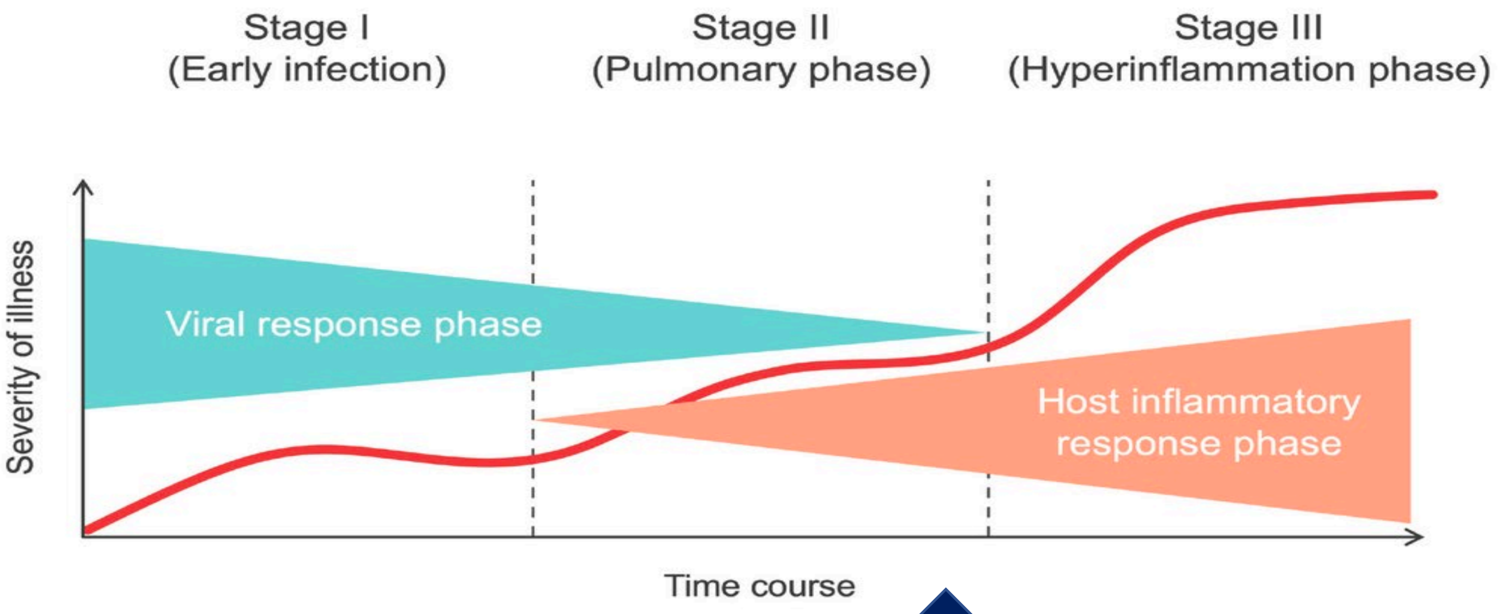
	Control	CFS
Total participants	35	52
Age (mean±SD)	36.6±12.0	42.8±13.7
Female/male ratio	27/8	44/8

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



Acute COVID

Post-COVID

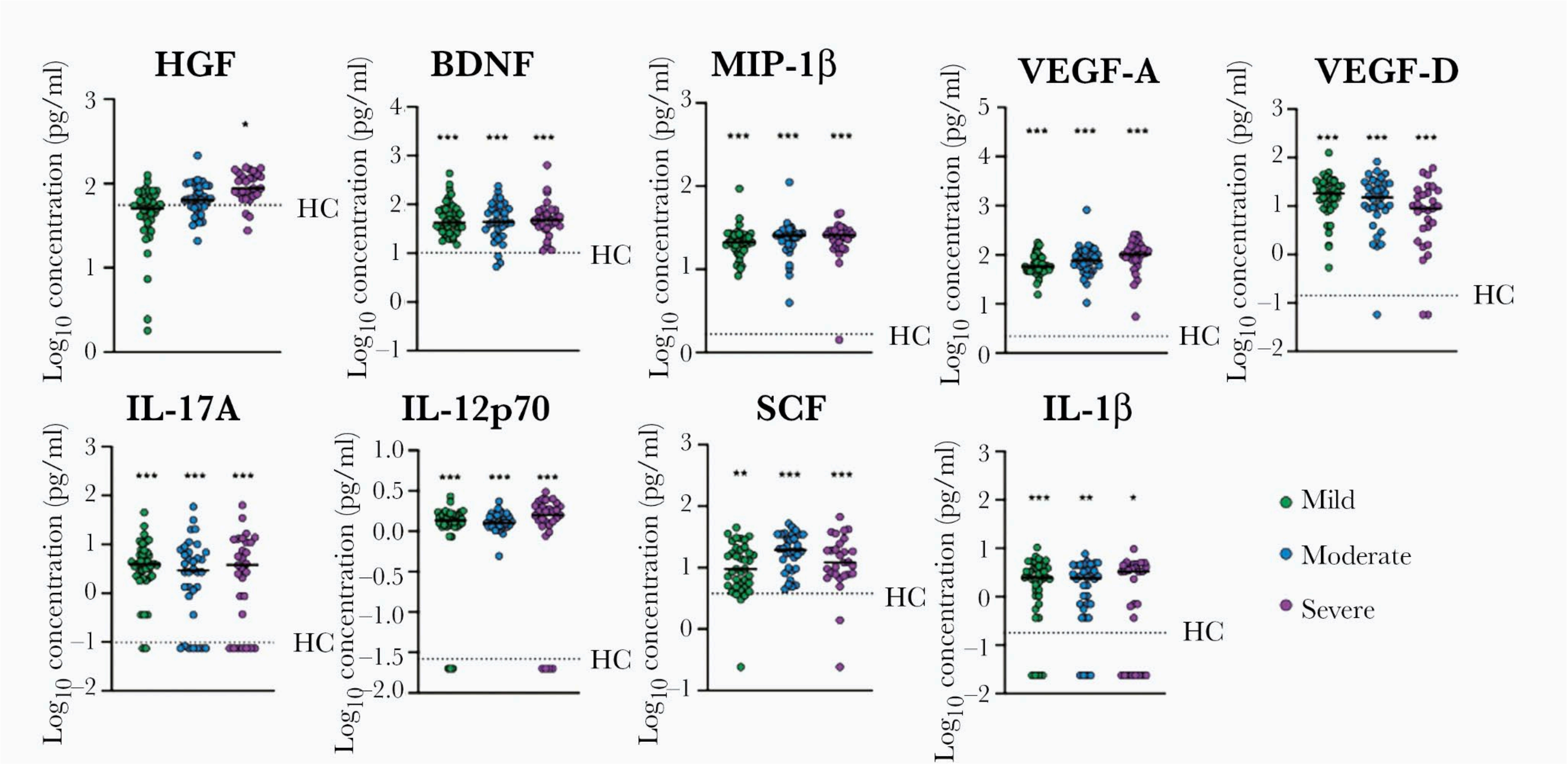


1,484 in hospitalized patients MSHS NYC with acute Covid-19 infection, **IL-6, IL-8 and TNF-α** levels predictors of patient survival ($P < 0.0001$, $P = 0.0205$ and $P = 0.0140$, respectively)

In severe COVID-19, TGFβ peak the first 2 weeks of infection profoundly inhibits NK cell function, prevent early viral control.
TGFβ is a hallmark of severe COVID-19

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.

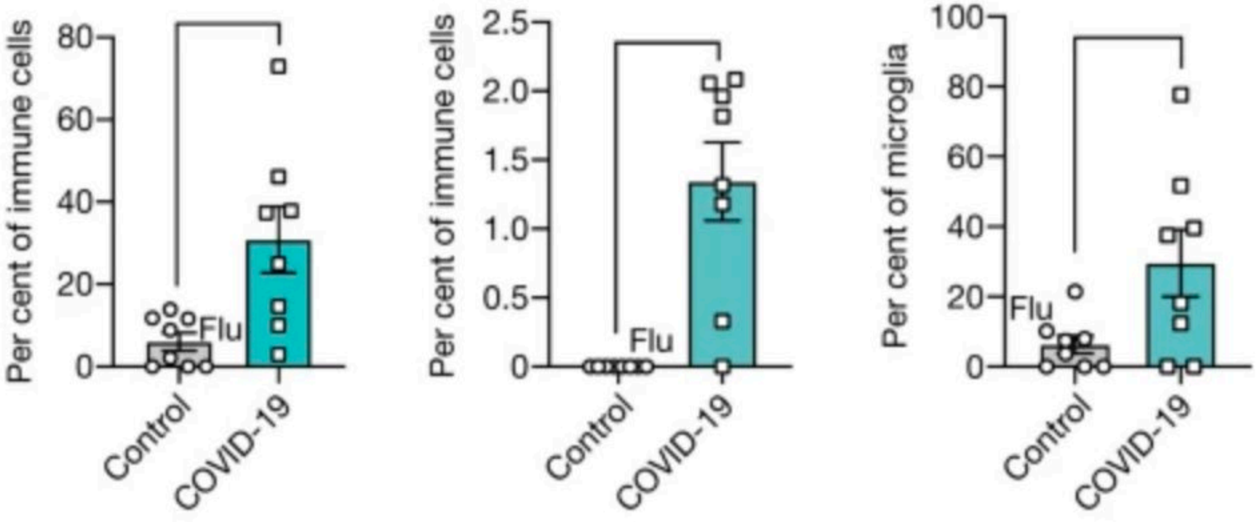
Neuroinflammation COVID-19

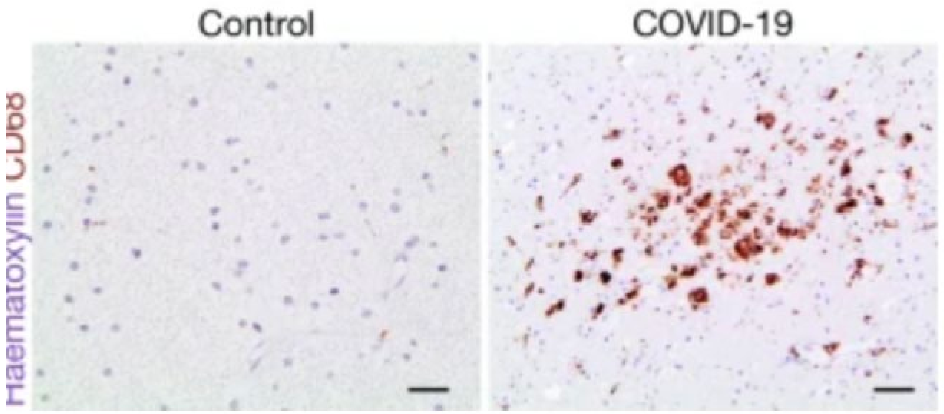
Neuroinflammation

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

american physiological society
AMERICAN JOURNAL OF PHYSIOLOGY
CELL PHYSIOLOGY

Am J Physiol Cell Physiol 320: C57–C65, 2021.
First published November 5, 2020; doi:10.1152/ajpcell.00426.2020

RESEARCH ARTICLE

Virus-Host Cell Interactions and the Viral Life Cycle: Basic Science to Therapeutics

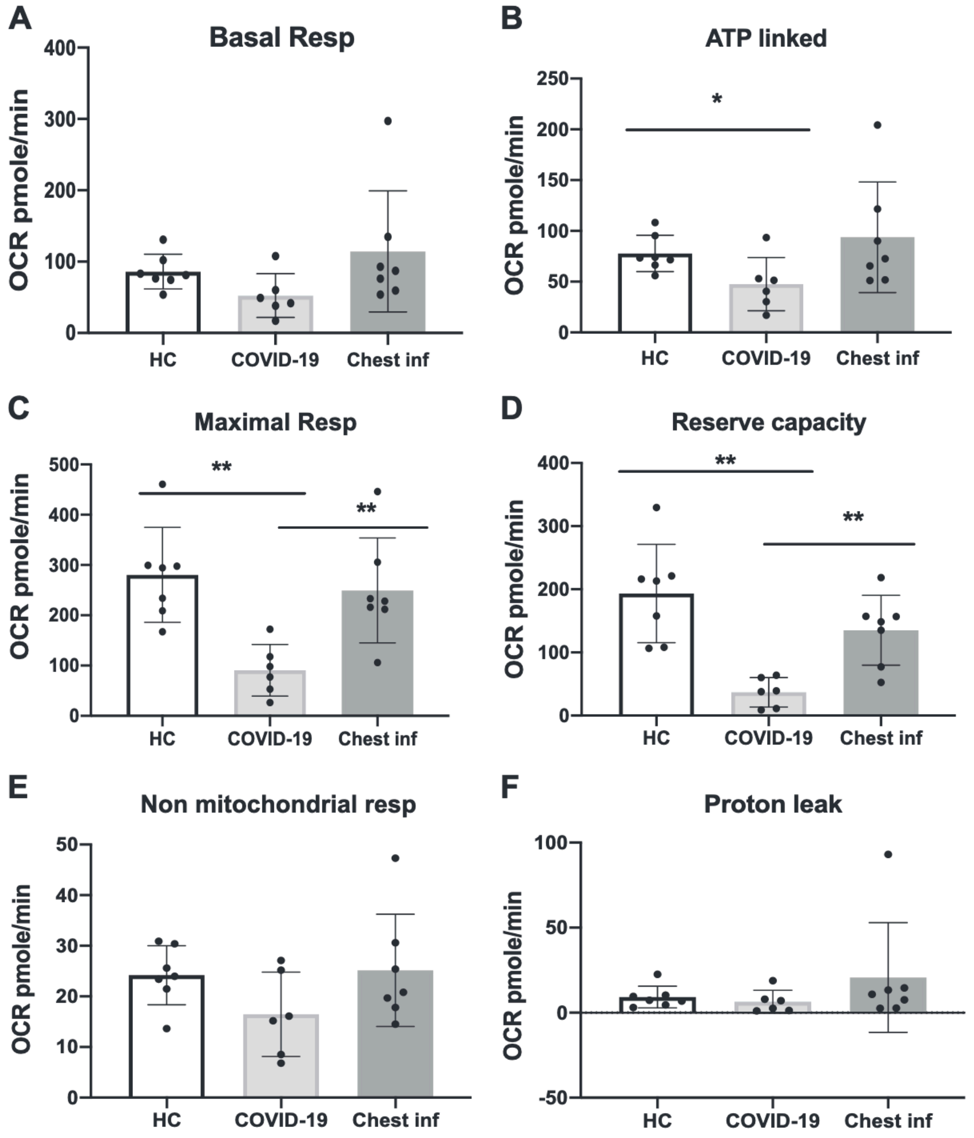
Mitochondrial metabolic manipulation by SARS-CoV-2 in peripheral blood mononuclear cells of patients with COVID-19

Saima Ajaz,[1] Mark J. McPhail,[1] Keshav K. Singh,[2] Salma Mujib,[1] Francesca M. Trovato,[1] Salvatore Napoli,[1] and Kosh Agarwal[1]

[1]Institute of Liver Studies, Kings College Hospital, London, United Kingdom; and [2]Department of Genetics, School of Medicine, The University of Alabama at Birmingham, Birmingham, Alabama

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



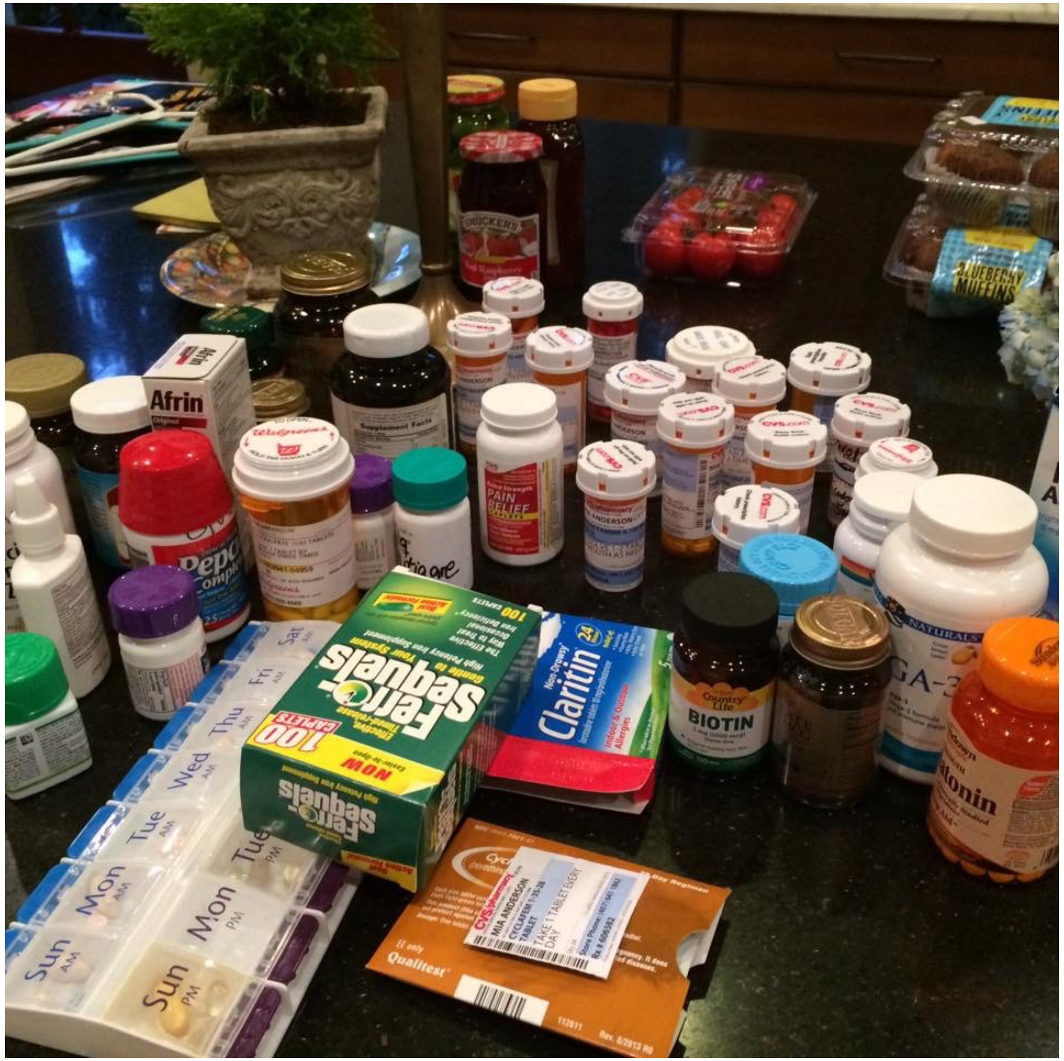
Conclusions

- 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)

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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)**

**hub/portal clinic*

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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


Thank You!