CDC Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Stakeholder Engagement and Communication (MECFS-SEC) Webinar/Conference Call

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The Biology of ME/CFS: Emerging Models

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The Biology of ME/CFS: Emerging Models

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September 16, 2019
Centers for Disease Control and Prevention Webinar

No significant conflicts of interest
An illness characterized by only symptoms and no consistent objective abnormalities:

- No consistent physical exam abnormalities
- No diagnostic tests
- No proven treatments
- No information on prognosis
- No evidence of underlying biological abnormalities

Hence, some wondered if it was really a disease
Cases differ from healthy controls (and sometimes disease comparison controls):

- Central and autonomic nervous system
- Metabolism (particularly energy metabolism)
- Immune phenotype and function
- Microbiome (?)
Neurologic Changes
Structural & Functional Brain Imaging
Autonomic abnormalities
CNS Involvement in ME/CFS

- **Neuroendocrine dysfunction**: Impairment of multiple limbic-hypothalamic-pituitary axes (involving cortisol, prolactin, & growth hormone) and serotonin (5-HT) system

- **Cognition**: Impairments in information processing speed, memory and attention—not explained by concomitant psychiatric disorders

- **Autonomic dysfunction**: Impaired sympathetic and parasympathetic function, 30-80%

- **MRI**: Multiple anatomic and functional abnormalities

- **SPECT**: Areas of reduced signal

- **PET**: Immune cell activation (neuroinflammation)

- **EEG abnormalities**: ↑sharp/spike waves, distinctive spectral coherence pattern, impaired connectivity
Brain Activation When Challenged
An fMRI (BOLD) Study During Stroop Test

When challenged, CFS pts equally accurate but much slower responses. And more brain areas (cortex and subcortical) are activated—esp. amygdala, hippocampus, basal ganglia, thalamus: the brain has to “work harder.”

MR Spectroscopy of the Brain Suggests Neuroinflammation

- 15 women with ME/CFS and 15 matched healthy controls
- Abnormalities were found in multiple brain regions, particularly left anterior cingulate
- Metabolite ratios in 7 regions correlated with fatigue
- Increased ratio of choline/creatinine, and increased lactate, were prominent findings

Metabolic Changes
Impaired ATP production
Hypometabolism
Oxidative/Nitrosative Stress
Impaired OxPhos in ME/CFS
Reduced Maximal Respiration (& 6 other measures)

Immunologic Changes

Differences in the numbers of different types of white blood cells

Altered function of certain white blood cells

Different levels of cytokines
Immunological Abnormalities in ME/CFS

- Increased levels of circulating immune complexes
- Increased levels of immunoglobulin G
- Decreased levels of certain IgG subsets
- Increased numbers of CD8+ “cytotoxic” T cells bearing activation antigens (CD38+, HLA-DR)
- Poorly functioning natural killer (NK) cells
- Increased blood levels of, and lymphocyte production of pro-inflammatory cytokines
Cytokine Findings

- **Blood** levels of many cytokines are significantly higher in ME/CFS patients than in healthy controls—in the first three years of illness, but not after\(^1\)

- Levels of many cytokines in *spinal fluid* also distinguish patients from healthy controls\(^2\)

- Levels of many circulating cytokines correlate positively with the severity of symptoms\(^3\)

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\(^1\)Hornig M, et al. Science Advances 2015 (Feb 27);1:e1400121


\(^3\)Montoya JG, et al. PNAS 2017;114:E7150-7158
Microbiome

Skew toward proinflammatory species

Evidence of “leaky gut”
How the Microbiome May Affect The Brain

• **The human microbiome:** Contains more than 100 times as many genes as we have human genes—a 2nd human genome, additional endocrine organ:

• **Microbial** genes produce molecules that affect human physiology:
  
  – Synthesize hormones and neurotransmitters (e.g. norepinephrine, serotonin, dopamine, ACh, GABA)

  – Synthesize molecules of inflammation (cytokines, prostaglandins) and elicit the production of inflammatory molecules by the gut immune system

  – Inflammation causes the gut to become “leaky”: the tight junctions that bind gut epithelial cells together become loosened — allowing bacteria and bacterial toxins to enter the blood, eliciting a systemic innate immune response

Exercise Causes Gut Bacteria to Enter the Blood in People with ME/CFS

Panel A

Firmicutes/Clostridia/.../LachnoXIVa

Post-Exertional Malaise
Effect of Exercise on Cognition

Number of testing errors with 3 repeated tests, pre- and post-exercise

Brain Activity Post vs. Pre-Exercise

Red=Working harder; Blue=Working less hard

Putting It All Together

Central & autonomic nervous system

Metabolism

White blood cell (immune system) types and function

Microbiome differences
Several Alternative Models

- Sickness behavior/inflammation\(^3,4,5\)
- Dauer/hibernation-torpor\(^6\)
- Cell danger response/incomplete healing\(^7\)
- Microbiome\(^8\)

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\(^5\) VanElzakker MB. Front Neurol 2019; 10.3389/fneur.2018.01033
\(^7\) Naviaux, R.K., Mitochondrion, 2018 https://doi.org /10.1016/ j.mito.2018.08.001
\(^8\) Nagy-Szakal D, et al. Microbiome 2017;5:44.
The Sickness Behavior/Inflammation Model for ME/CFS

What do we feel like when we’re sick?
Sick Puppy!
Sickness Behavior

• Seen in most animals, even invertebrates

• A temporary response to injury and infection: to focus body’s energy stores on fighting infection & healing injury (acute inflammation & fever) the brain decreases energy-consuming activities: lethargy, social withdrawal, achiness, sleepiness, loss of libido, difficulty thinking, depression, anorexia

• Are there circumstances in which this acute physiology could become chronic, with sickness symptoms becoming chronic?

Neuroinflammation in ME/CFS

Activation of the innate & adaptive immune systems by stimuli both inside & outside the brain.
What Causes the Symptoms of ME/CFS?

Speculative Model: Many Triggers, Final Common Pathway

Fatigue nucleus: in basal ganglia/ prefrontal cortex/ ant. cingulate?

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What Causes the Symptoms of ME/CFS?

Speculative Model: Many Triggers, Final Common Pathway

- Infection of the brain
- Auto-Abs
- Toxins
- Obesity
- Chronic stress
- Leptin ↑

Activation of brain’s innate immune system (e.g., microglia) yields cytokines that trigger fatigue nucleus.

Fatigue nucleus: in basal ganglia/prefrontal cortex/ant. cingulate?

Infection/inflammation elsewhere in the body, signaling the brain.

How Can Inflammation Outside the Brain Activate the Innate Immune System Inside the Brain? -part 1

Innate immune system in the brain can be activated by infection elsewhere in the body due to:

- **Humoral:** A blood-brain barrier made “porous” by inflammation, allowing entry into the brain of circulating immune cells and molecules (via circumventricular organs and brain endothelial cells)

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- **Neural:** Peripheral inflammation triggers retrograde signals up the vagus nerve to the brain

What Triggers Neuroinflammation?

Chronic, low-grade infection of the brain

Inflammation elsewhere in the body, such as caused by the gut microbiome
Metagenomic Gut Microbiome Study

- 50 ME/CFS and 50 matched healthy controls

- Relative abundance of several genera were significantly associated with ME/CFS: pro-inflammatory bacteria increased anti-inflammatory bacteria were decreased.

- Several bacterial metabolic pathways also were significantly associated with ME/CFS

- The relative abundance of those bacterial taxa, and those same bacterial metabolic pathways, not only were associated with ME/CFS: they also were positively correlated with the severity of symptoms—particularly fatigue and pain

From: Nagy-Szakal D…Lipkin WI. Microbiome 2017;5:44
Gut Barrier Damage May Trigger Innate Immunity

Breach in gut barrier ➞ LPS translocate to blood ➞ LPS binding protein (LBP) up + sCD14 (LPS-LBP receptor) up: Triggering innate immunity

Depressed Metabolism:
The Hibernation-Torpor/Dauer Model for ME/CFS
What Purpose is Served by Dauer and Hibernation/Torpor?

• Worms can enter a state called dauer, and larger animals (including mammals) can enter a state called hibernation/torpor—a temporary state prompted by harsh environmental conditions that helps an animal survive, but at the expense of considerably reduced functional capacity.

• Energy-requiring reactions, and the need for oxygen as a source of energy, are reduced to a bare minimum.
Similarities: Dauer and Hibernation/Torpor

Both states

• Are regulated by genes that also are involved in oxidative stress & innate immunity\(^1\)

• Involve increased glycolysis and decreased aerobic respiration\(^2\)

• May involve alterations in the microbiome\(^3\)

• Allow only essential energy-requiring functions: hypometabolic\(^4\)

• Are reversible, and controlled by autonomic NS\(^5\)

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\(^1\) Lin XX. Nat Commun 2018;9/10.1038/s41467-018-06624-0.


Can the Different Models Be United?
Uniting These ME/CFS Disease Models

- Sickness behavior from neuroinflammation and dauer/hibernation-torpor involve ancient biological mechanisms that preserve energy in order to prevent or heal injury, but at the expense of temporarily impaired function.

- The microbiome may be causing inflammation/injury in some patients.

- Do the symptoms of ME/CFS result from activation of these ancient mechanisms, and a pathological inability to turn them off?
In Summary...

• There is robust evidence of underlying abnormalities in patients with ME/CFS

• Those abnormalities have considerable overlap with several well documented models of disease

• More needs to be done to solidify and expand our understanding of each of these abnormalities, and of their relationship with each other...and of the triggers that set them all in motion
A Possible Diagnostic Test for ME/CFS

Mononuclear white blood cells from 20 people with ME/CFS, but not from 20 healthy controls, develop increased electrical impedance with osmotic stress.

From: Esfandyarpour R...Davis RW. PNAS 2019;116:10250-7
RBCs Are Stiffer and Transit Microcirculation More Slowly in ME/CFS

Neuroinflammation in Fibromyalgia
Diffuse Activation of Glial Cells by PET Scan, Especially Frontal and Parietal Lobes, Correlating with Fatigue

MGH & Karolinska Institute