Will COVID-19 Lead to ME/CFS in Some People?

Anthony L. Komaroff, MD
Professor of Medicine, Harvard Medical School
Senior Physician, Brigham and Women’s Hospital

Solve ME/CFS Initiative Webinar
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No conflicts of interest
# COVID-19 Statistics As Of 8/23/20

<table>
<thead>
<tr>
<th>United States</th>
<th>World</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cases</td>
<td>5.6 million</td>
</tr>
<tr>
<td>Total Deaths</td>
<td>176,248</td>
</tr>
</tbody>
</table>

*From: New York Times/WHO/CDC*
# Of COVID Cases, By Country: Trend Over Past 7 Months

From: NY Times/WHO/CDC
January 20, 2020: The First Cases of COVID-19 in the USA and S. Korea
# How Are We Doing: USA vs S. Korea

## # Cases and # Deaths/100,000 people

*First cases of COVID-19: January 20, 2020*

<table>
<thead>
<tr>
<th>South Korea</th>
<th>USA</th>
<th>USA Higher Times...</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases/100,000</strong></td>
<td>34</td>
<td>1,737</td>
</tr>
<tr>
<td><strong>Deaths/100,000</strong></td>
<td>&lt;1</td>
<td>54</td>
</tr>
</tbody>
</table>

*From: NY Times/WHO/CDC*
Have Lockdowns, Social Distancing, Masks, Etc. Achieved Anything?  
*U.S., China, S Korea, Italy, Iran, France*

<table>
<thead>
<tr>
<th></th>
<th>United States</th>
<th>All 6 Countries</th>
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</thead>
<tbody>
<tr>
<td><strong># Cases Averted</strong></td>
<td>60 million</td>
<td>495 million</td>
</tr>
<tr>
<td><strong># Deaths Averted</strong></td>
<td>300,000*</td>
<td>~2.5 million*</td>
</tr>
</tbody>
</table>

Hsiang S et al. *Nature* 2020 Jun 8; [e-pub]. ([https://doi.org/10.1038/s41586-020-2404-8](https://doi.org/10.1038/s41586-020-2404-8))

* Assumes 0.5% mortality rate, a conservative estimate
What Are COVID's Effects On the Body?
What Are COVID’s Effects On the Body?
What Are COVID’s Effects On the Body?
Coronavirus Infection of the Heart

SARS-CoV-2 in heart muscle

Activated lymphocytes in heart muscle

And Puntmann VO, et al. JAMA Cardiology 2020 (pub. Online 7/27/20)
What Are COVID’s Effects On the Body?
What Are COVID’s Effects On the Body?

The Brain

BRAIN

LUNGS

LIVER

KIDNEYS

HEART

STOMACH

SMALL INTESTINE

LARGE INTESTINE
Neuroinflammation

Activation of the innate & adaptive immune systems by stimuli both inside & outside the brain

Courtesy of David Systrom, MD
What Happens to Someone Who Contracts the COVID Virus?

- Absolutely nothing: no symptoms, no lingering illness
- Mild symptom: cough, fever, achiness
- More serious symptoms: breathlessness, high fevers, exhaustion—monitored closely at home
- Hospitalization, supplemental oxygen ± ventilator
- Lung failure, kidney failure, heart failure, strokes
- Death
What Happens to Someone Who Contracts the COVID Virus?

• Mild symptom: cough, fever, achiness
  Recovery OR Long hauler

• More serious symptoms: breathlessness, high fevers, exhaustion—monitored closely at home
  Recovery OR Long hauler

• Hospitalization, supplemental oxygen ± ventilator

• Lung failure, kidney failure, heart failure
The “Long Haulers”

- Many COVID-19 patients recover completely: back to prior state of health
- Recover almost: mild residual symptoms
- Recover a little: severe residual symptoms that meet criteria for ME/CFS; and/or with chronic lung, heart, kidney or brain dysfunction
The Story of Two COVID-19 Patients

Middle-aged man, mild COVID pneumonia

- Sleeps all day, cannot work: a long hauler
- Has minimal lung damage, and feels fine

Elderly woman with leukemia and arterial disease: becomes severely ill from COVID, has cardiac arrest, is resuscitated, finally leaves the hospital

From: Couzin-Frankel J. Science 2020;369:614
Why Can Outcomes Be So Different?

• The amount of virus that enters the body
• Inherited genes that make us more or less vulnerable
• Chronic illnesses (like high blood pressure, obesity) that make us more vulnerable
• The quality of medical care
So COVID-19 can affect many organs, but what’s the evidence that it can cause ME/CFS?
Why Might ME/CFS Develop After COVID?

• ME/CFS often, but not always, begins as an apparently infectious illness—symptoms like a “cold” or “flu”

• ME/CFS can develop after well documented acute infections, even when those infections have been properly diagnosed and treated
Infections That Can Be Followed by ME/CFS or Similar Chronic Illness

- 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 herpes-6\(^10\)
- Ebola\(^11\)
- West Nile Virus\(^12\)
- SARS\(^13\)
- Dengue\(^14\)
- Parvovirus\(^15\)
- COVID-19???

\(^2\) Poskanzer DC, et al. NEJM 1957;257:356.
\(^3\) Acheson ED. Am J Med 1959;4:569.
Fatigue And Infections

- Fatigue is common during many acute infections, including almost all types of pneumonia

- Some level of fatigue can persist for a while after infections have been properly treated

- Debilitating fatigue (and other symptoms) can last months/years following some infections (post-infectious fatigue)
Persistent Fatigue Following Non-COVID Pneumonia

Fatigue Severity

Why Might ME/CFS Develop After COVID?

• Because it is looking like it does:

“It’s extraordinary how many people have a postviral syndrome that’s very strikingly similar to myalgic encephalomyelitis/chronic fatigue syndrome. They just don’t get back to normal energy or normal feeling of good health.”

-- Dr. Anthony Fauci, Medscape Interview
IOM/CDC Case Definition of ME/Chronic Fatigue Syndrome

1. Substantial impairment in the ability to function at home or at work, lasting *for more than 6 months*, accompanied by profound fatigue, of new or definite onset (not lifelong), not substantially alleviated by rest AND

2. Post-exertional malaise AND

3. Unrefreshing sleep

PLUS at least one of:

4. Cognitive impairment OR

5. Orthostatic intolerance

*Redefining an Illness. Institute of Medicine, 2015.*
So Does ME/CFS Follow COVID-19?

• Although the COVID pandemic began in December, most cases have begun only in the past 2-3 months in the U.S.

• So it will take several more months before we are in a position to know if ME/CFS—according to case definitions—develops post-COVID, and how often

• But what do we know so far?
Continued Symptoms in Adult Outpatients Testing Positive For COVID-19

From: Tenforde MW, et al. MMWR July 24, 2020
Continued Symptoms in Adult Outpatients Testing Positive For COVID-19

% Who Did Not Return to Usual Health 2-3 Weeks Later

By Age

- 18-34
- 35-49
- 50 +

By # of Chronic Illnesses

- 0-1
- 2
- 3+

From: Tenforde MW, et al. MMWR July 24, 2020
143 definite COVID-19 patients, now free of virus
• Mean age 56.5 years
• 37% women
• 20% low oxygen levels

60 days after getting sick:
• 55% had at least 3 ongoing symptoms (none fever)
• 41% had worsened quality of life

From: Carfi A, et al. JAMA 2020;324:603
Survey of Facebook Survivors Group

50 Most Common Long Hauler Symptoms

- Fatigue
- Muscle or body aches
- Shortness of breath or difficulty breathing
- Difficulty concentrating or focusing
- Inability to exercise or be active
- Headache
- Difficulty sleeping
- Anxiety
- Memory problems
- Dizziness
- Persistent chest pain or pressure
- Cough
- Joint pain
- Heart palpitations
- Diarrhea
- Sore throat
- Night sweats
- Partial or complete loss of sense of smell

From: Survivor Corp Facebook group survey, N=1,567, Indiana U School of Medicine
COVID Support Group*

- Online survey of 1500 people with confirmed or suspected COVID-19, mostly from U.S. or U.K.
- 82% reported symptoms lasting over 2 months; 54% with symptoms > 3 months
- 80% between ages of 30-60
- 41% felt the doctors had not listened to or believed them

* Reported by “long hauler” Karyn Bishof
Being Taken Seriously

When First Becoming Sick

• People with COVID-19 were disbelieved in February – May because doctors didn’t yet realize how many organs could be affected and symptoms caused.

• The failure of enough accurate testing caused many to be misdiagnosed.

Subsequently

• “You can’t still have COVID...when the virus leaves your body you’re better.”

• “There is no documented lingering illness after COVID: it’s not in the textbooks.”

From: Yong E. Long-haulers are redefining COVID-19. The Atlantic 8/20
Body Politic COVID Support Group

**Neurologic Symptoms**
- Extreme, persisting fatigue (91%)
- Headaches (88%)
- Poor quality sleep (84%)
- Lack of concentration (86%)

**Heart Symptoms**
- Palpitations (73%)
- Chest pain (77%)

**Lung Symptoms**
- Cough (70%)
- Shortness of breath (87%)
So A State of Chronic Fatigue
And Other “ME/CFS Symptoms”
Can Follow COVID-19

What is the biological explanation?

Is it the same biological explanation as in people with ME/CFS that did not start with COVID-19?
ME/CFS is like the flu, but like a flu that never goes away.

-- Many, many patients
What do we feel like when we get the flu....

why do we feel that way...

and why does it go away?
Hard-Wired Sickness Symptoms: A Hunkering Down Mechanism

- Seen in most animals, even invertebrates

- A temporary, acute response to injury and infection: the brain decreases energy-consuming activities causing lethargy, social withdrawal, achiness, sleepiness, loss of libido, difficulty thinking, depression, reduced appetite – to focus body’s energy stores on fighting infection & healing injury. When injury/ infection are healed, the behavior is turned off.

- Are there circumstances in which this acute physiology could become chronic, with sickness symptoms becoming chronic: not turned off?

What Causes the Symptoms of ME/CFS?
Speculative Model: Many Triggers, Final Common Pathway

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

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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, hypothalamus?

Theory: Activation of the brain’s immune system (neuroinflammation) stimulates a “fatigue nucleus” (a group of neurons) to cause all of the symptoms of an acute infection like the flu, and possibly of ME/CFS. So:

1. Is there evidence of neuroinflammation in ME/CFS and does it cause fatigue?

2. Is there a fatigue nucleus, and where is it?
PET Evidence of Brain Inflammation Distinguishes ME/CFS from Healthy


MR Spectroscopy of the Brain Suggests Neuroinflammation

15 women with ME/CFS and 15 matched healthy controls
MR spectroscopy of the whole brain measuring metabolic markers of inflammation and temperature

↑ choline/creatinine most prominent in left anterior cingulate (region that responds to ↑ inflammatory cytokines by causing fatigue and pain)

Metabolite ratios in 7 regions correlate with fatigue

Increased temperature and lactate throughout brain

Neuroinflammation (activation of microglia and astrocytes), particularly in substantia nigra, correlates with fatigue score (P=0.002), and not with number of MS lesions or brain atrophy.
1. So neuroinflammation does appear to be a cause of fatigue?

2. Is there a fatigue nucleus, and where is it?
Location Of A Torpor Nucleus in Mice

Hypothalamus, preoptic area, specific population of neurons, specific neurotransmitters, control entry and exit from torpor

What **Starts** the Sickness Symptoms?

- Stimulation of a fatigue nucleus by an activated immune system in the brain (neuroinflammation) is very plausible.
- But what **ends** sickness symptoms, when we get a normal **flu** and...
- Why is it that the sickness symptoms **don’t end** when a person gets ME/CFS?
What **Starts** the Sickness Symptoms?

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- Why is it that the sickness symptoms **don’t end** when a person gets **ME/CFS**?
But Don’t Misunderstand....

- I’m not saying that the theory of neuroinflammation stimulating a fatigue nucleus is the only reason for ME/CFS
  - Autoimmunity
  - Impaired energy metabolism/oxidative stress
  - Immune system abnormalities
  - Autonomic nervous system abnormalities
  - Other?
Neuroinflammation

Immune abnormalities

Continuous stimulation of the fatigue nucleus

Defective energy metabolism

Autonomic abnormalities

Autoimmunity

Other?
Neuroinflammation

Autoimmunity

Continuous stimulation of the fatigue nucleus

Defective energy metabolism

Immune abnormalities

Autonomic abnormalities

Other?
Conclusions

• There probably will be a post-COVID form of ME/CFS

• It is very important to study it:
  • to learn about and help treat the post-COVID condition
  • and possibly to learn more about ME/CFS not related to COVID-19

• The technology available today to understand the underlying biology of ME/CFS is remarkable
Questions to Study

• How common is post-COVID-19 ME/CFS?
• How long does it last?
• What happens when a person with ME/CFS gets COVID-19: Symptoms, laboratory test/biological changes?
• Are there differences between people with ME/CFS and people without ME/CFS when they get COVID-19:
  o Are people with ME/CFS more or less vulnerable to getting COVID-19?
  o Are neurological, metabolic, and immunologic findings different?
Final Remarks

- A remarkable amount of media attention post-COVID “long haulers”: renewed interest in ME/CFS
- Studies of long-haulers are underway all over the world – U.S., U.K., China, elsewhere
- Once again, one reason for this interest is an activated community of people afflicted by the illness – people studying it on their own, and pushing the biomedical community to study it.
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“A lot of people who don’t have the energy to educate the world are educating the world.”

-- Lauren Nichols*

From: Yong E. Long-haulers are redefining COVID-19. The Atlantic 8/20
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