Post COVID "long haulers" and post viral ME/CFS: Lessons from post viral illness

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INSTITUTE FOR NEURO IMMUNE MEDICINE: MOVING KNOWLEDGE TO TREATMENT

NANCY KLIMAS MD ON BEHALF OF THE INIM TEAM

NOVA SOUTHEASTERN UNIVERSITY

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ME/CFS

- ME/CFS is most frequently post viral, predicted by the severity and the immunogenicity of the triggering virus. Environmental triggers are also described.
- More frequent in women than men, with >1M cases in the USA

ME/CFS Case Definition (IOM)

- A substantial reduction in activity
  - 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* post exertional malaise
- *And* unrefreshing sleep
- *Either* cognitive impairment or orthostatic intolerance

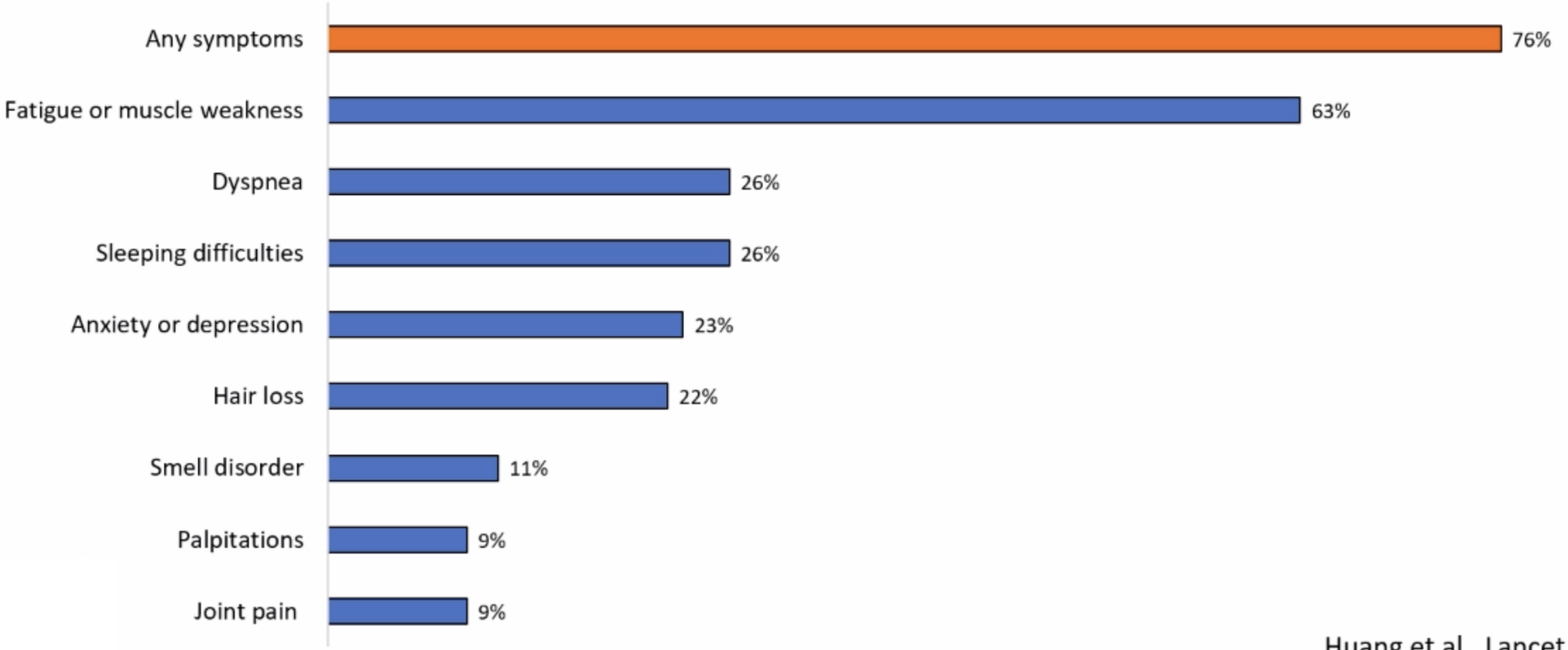
- **Wu et al. (2017, Nature Sci Rep):** 25 people with SARS **12 years** after recovery: 68% had hyperlipidemia, 44% had cardiovascular system abnormalities and 60% had glucose metabolism disorders.
- **Li et al. (2004, Paediatric Respiratory Reviews):** at **6 months** post recovery, 34% of childre had abnormal CT images (i.e., ground-glass opacities, air trapping), some had abnormal lun function tests & exercise impairment
- **Lam et al (2009, Arch Intern Med.):** 40% of people recovering from SARS reported chronic fatigue symptoms **3.5 years** after being diagnosed
- **Moldofsky & Patcai (2011, BMC Neurol.)**: 22 people with SARS-CoV-1 in Toronto, who remained unable to work **13–36 months** after infection, had persistent fatigue, muscle pain depression and disrupted sleep compared with matched controls.
- **Zhang et al (2020, Bone Res.): after 15 years**, 4.6% of SARS patients still had visible lesion on their lungs and 38% had reduced diffusion capacity.

Long Term Sequelae from SARS COV-1

Long COVID often presents as reported persistent severe fatigue, headaches, and brain fog (subjective cognitive impairment) for greater than 4 weeks after acute illness and may be independent of illness severity.
- Greenhaigh et al, BMJ 2020

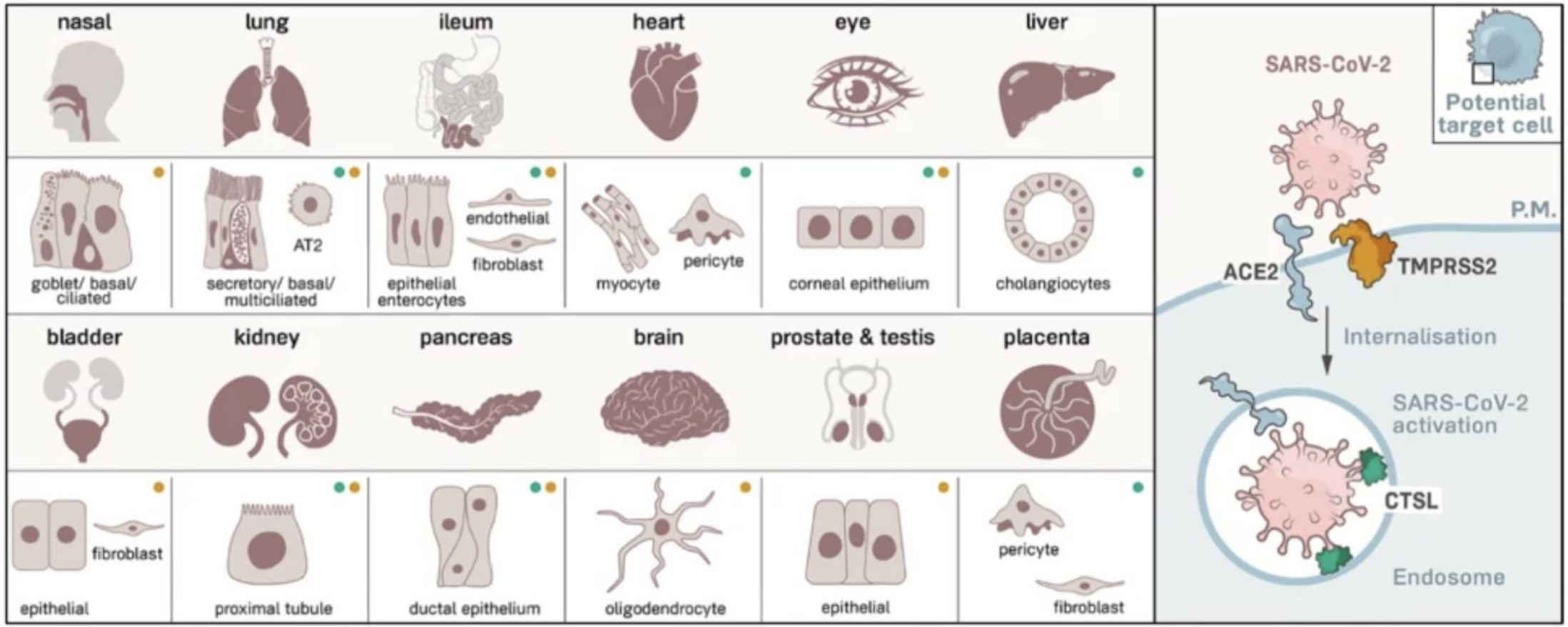
Three quarters of patients hospitalized with COVID-19 had **at least one ongoing symptom** 6 months after their acute illness.

Symptoms among 1,733 patients after hospitalization for COVID-19, China

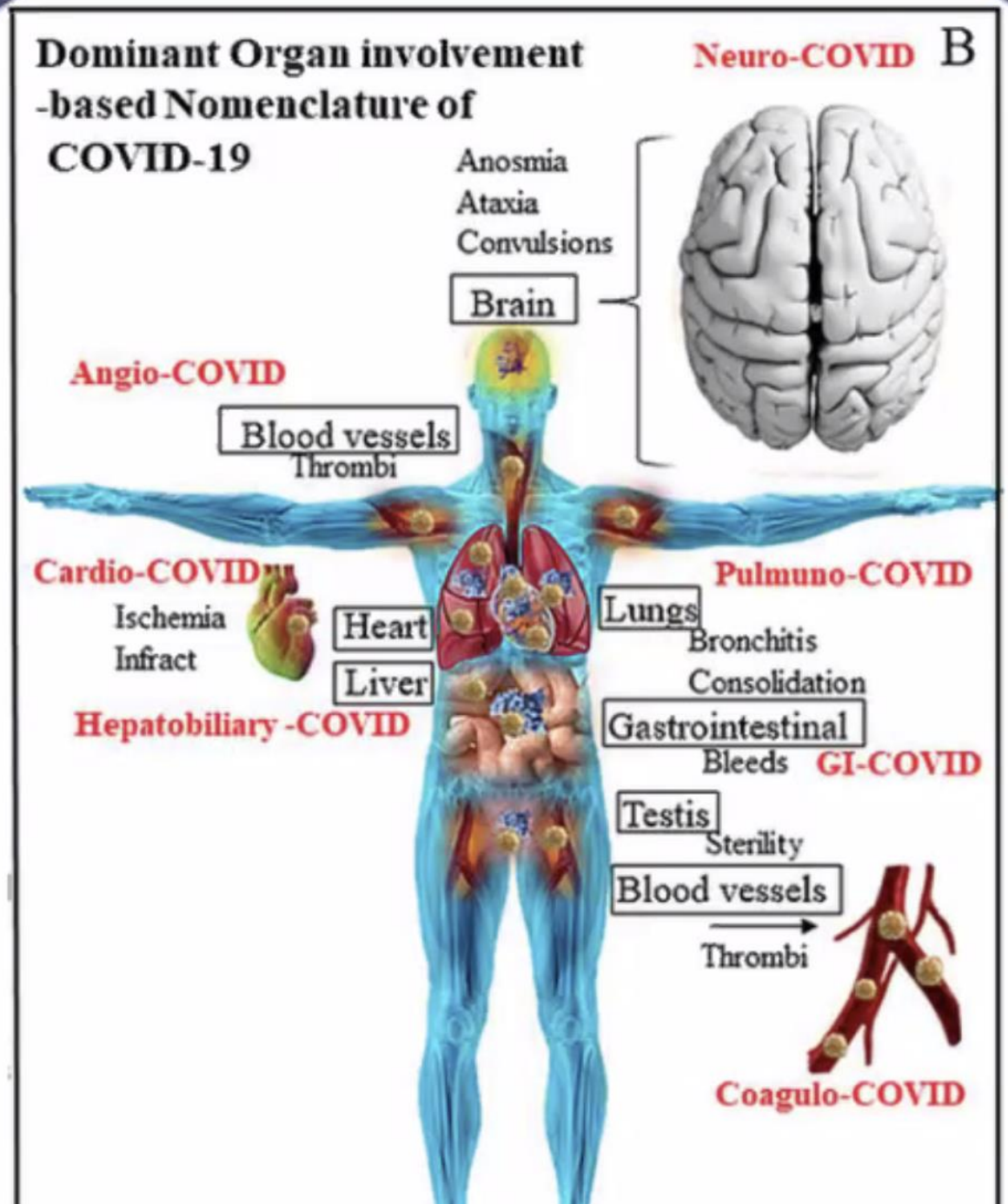


Huang et al., Lancet. 2021

COVID-19 Affects Multiple Organs

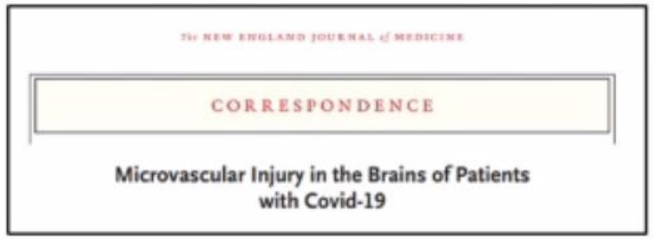


The Scientist, April 2020

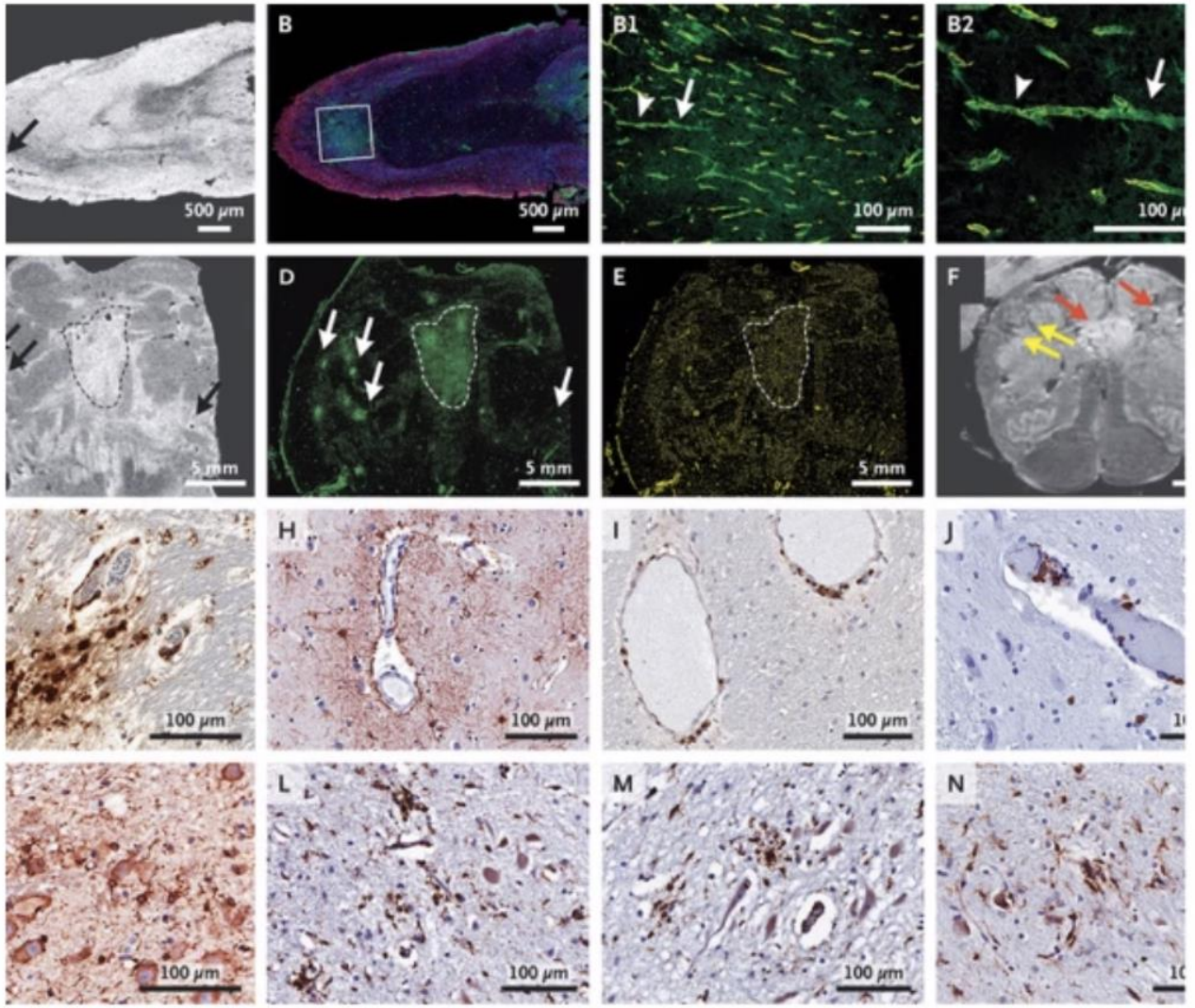

Dominant Organ involvement -based Nomenclature of COVID-19
B
Neuro-COVID
Anosmia
Ataxia
Convulsions
Brain
Angio-COVID
Blood vessels
Thrombi
Cardio-COVID
Ischemia
Infract
Heart
Liver
Hepatobiliary -COVID
Pulmuno-COVID
Lungs
Bronchitis
Consolidation
Gastrointestinal
Bleeds
GI-COVID
Testis
Sterility
Blood vessels
Thrombi
Coagulo-COVID

Is SARS-CoV-2 in the brain?

- Post-mortem study of brains of individuals who had COVID-19
- No evidence of viral infection in brain
- Widespread evidence of inflammation and damage, including:
    - Multifocal breakdown of the blood brain barrier, small infarcts, microhemorrhages, inflammatory infiltrates, and microglial nodules,
- Infection can lead to blood clots → stroke

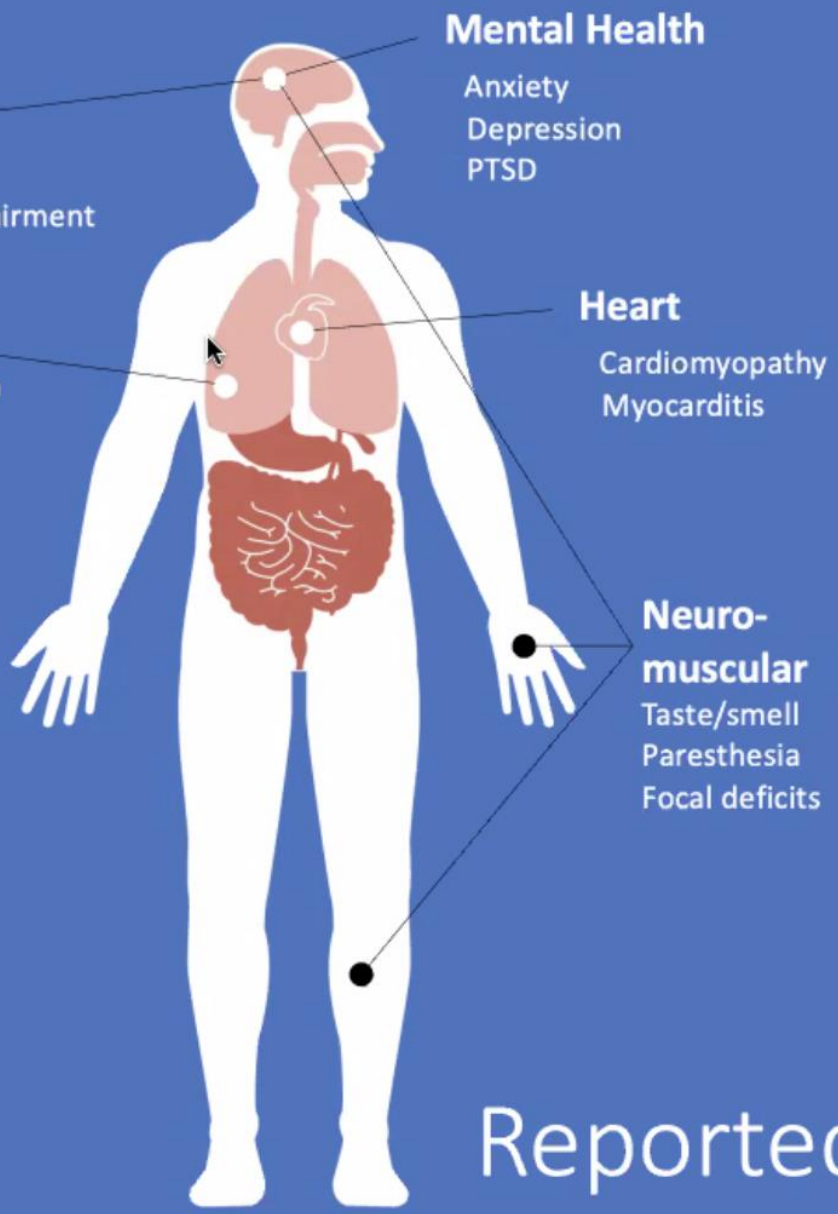


Nath et al, *NEJM*, NINDS



Pathological Studies of Microvascular Injury in the Brains of Patients Who Died from COVID-19

Long(er) term sequalae



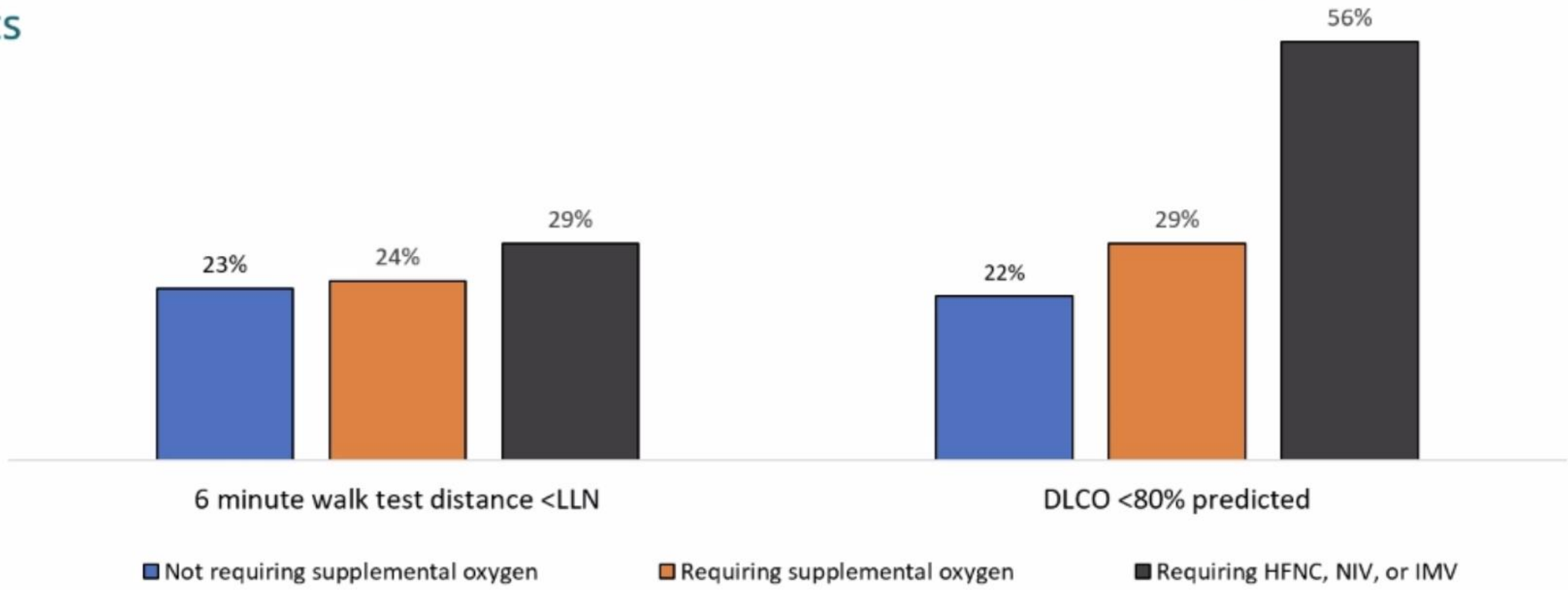
Post-COVID Syndrome - "Long-hauler"

- Waxing and waning
- Fatigue
- Paresthesia
- Cognitive impairment
- Dyspnea
- Palpitations

Reported Outcomes

One in five patients **not requiring supplemental oxygen** during hospitalization **had decreased lung function** after 6 months.

Pulmonary function and 6-minute walk test distance results among COVID-19 hospitalized patients

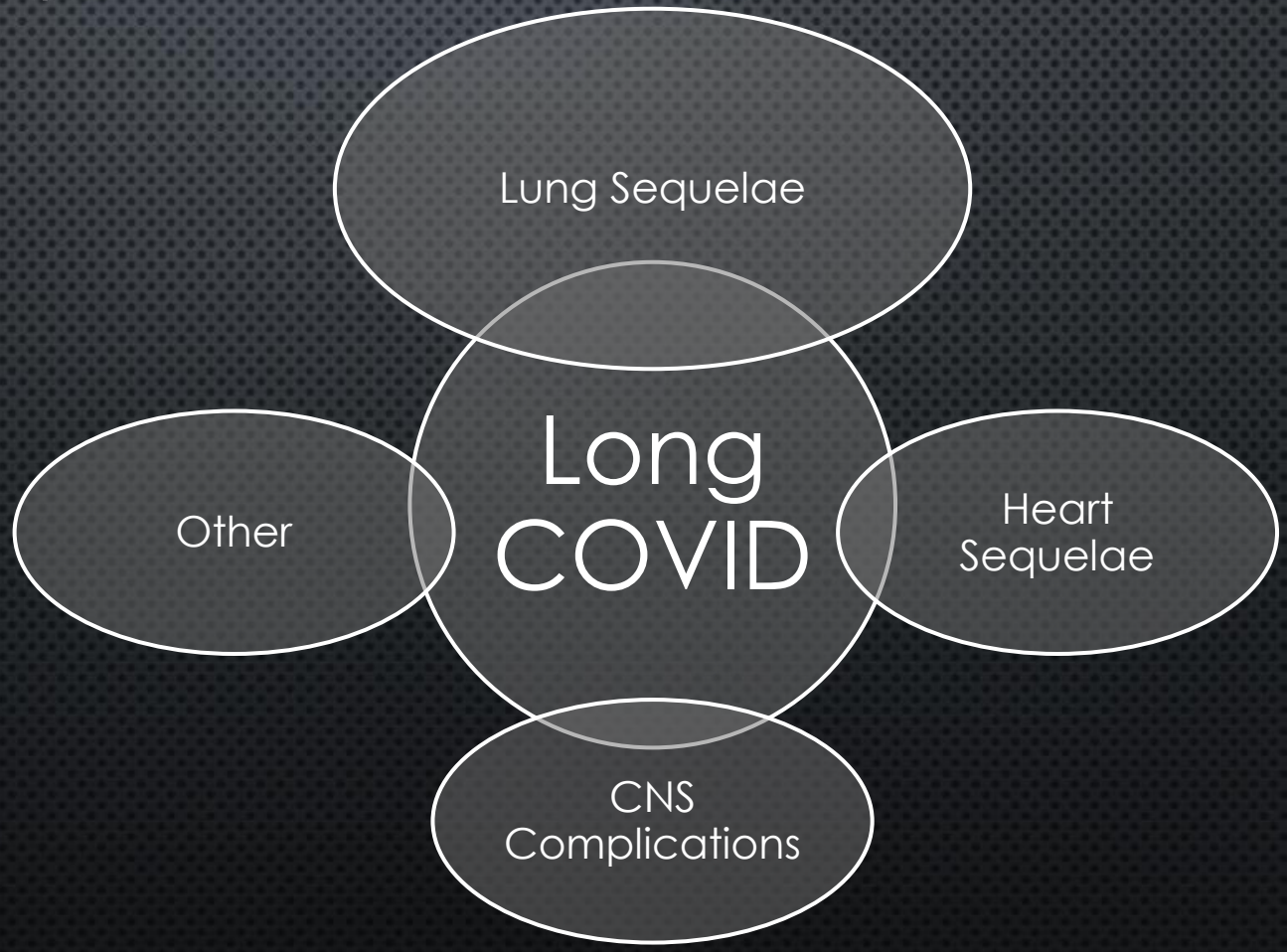


LLN = lower limit of normal; DLCO = diffusion capacity for carbon monoxide

Huang et al., Lancet, 2021

LONG COVID SYMPTOMS MAY OVERLAP WITH OTHER COMPLICATIONS OF ACUTE COVID

Long COVID frequently occurs after mild to moderate acute COVID, while organ specific long term sequelae is more common in hospitalized (severe) acute COVID



Progression of PD 3 months after acute COVID

- We report that the most common long-term effects of COVID-19 are worsening of motor function (51.9%) and increased levodopa daily dose requirements (48.2%) followed by fatigue (40.7%); cognitive disturbances (22.2%), including "brain fog", loss of concentration and memory deficits; and sleep disturbances (22.2%),
- Severity of acute COVID not predictive
- Leta V, Rodríguez-Violante M, Abundes A, et al. Parkinson's Disease and Post-COVID-19 Syndrome: The Parkinson's Long-COVID Spectrum. *Mov Disord*. 2021;36(6):1287-1289. doi:10.1002/mds.28622

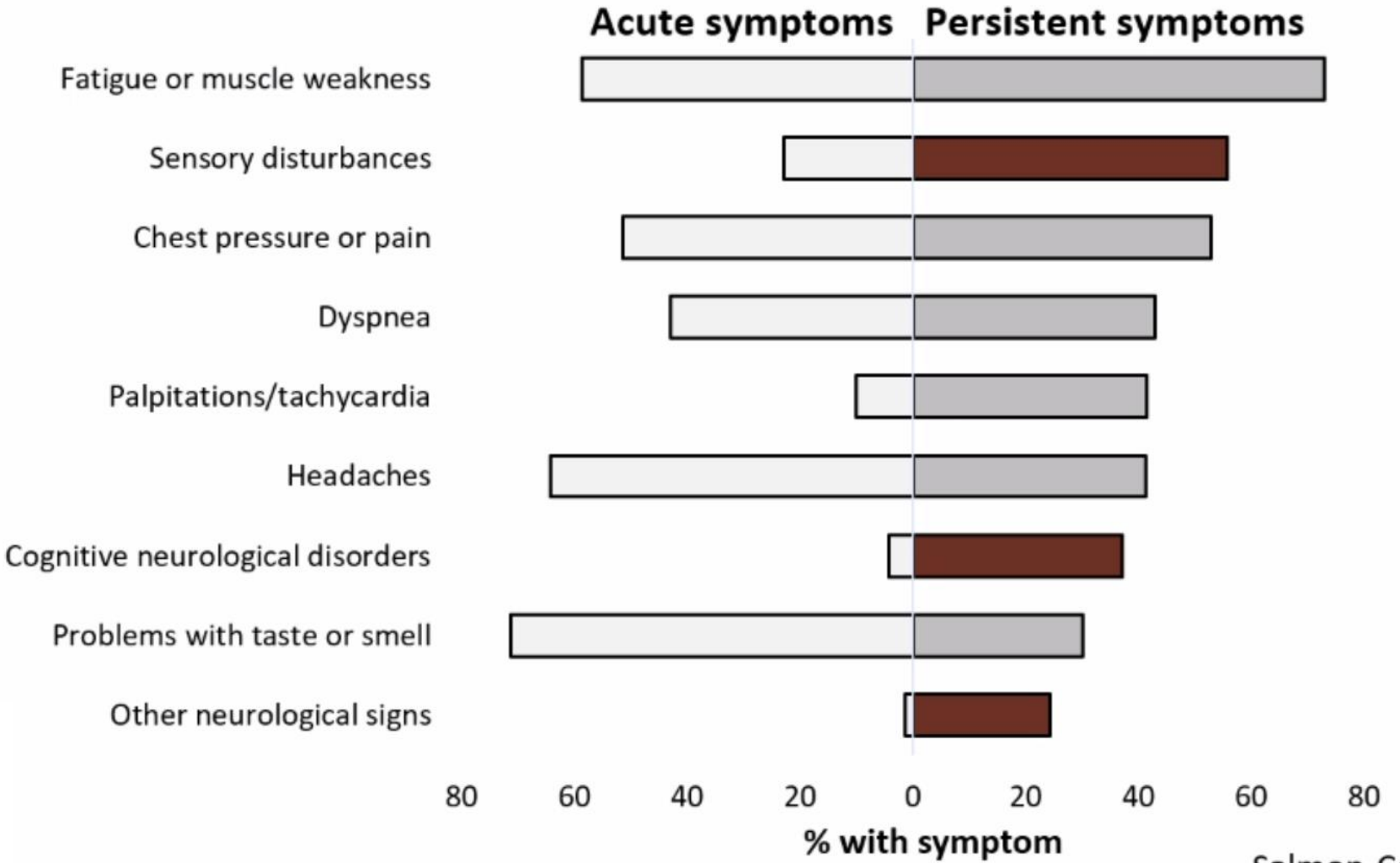
Prolonged symptoms are common among patients with mild COVID-19 disease **not requiring hospitalization**.

- Survey of patients in a post-COVID 19 clinic in France[1] and telephone surveys in the Faroe islands[2] and Switzerland[3]
  - 35-54% of patients with mild acute COVID-19 had **persistent symptoms after 2-4 months**
  - 50-76% of patients **reported new symptoms** not present in their acute COVID-19 illness **or symptoms that resolved and reappeared**[1]
  - 9% reported prolonged symptoms as **severe**[2]

1. Salmon-Ceron et al., J Infect. 2020
2. Petersen et al., Clin Infect Dis. 2020
3. Nehme et al., Ann Intern Med. 2020

More than one quarter of patients **developed new neurological symptoms** after their acute COVID-19 illness.

COVID-19 symptoms among 70 non-hospitalized patients, France



Salmon-Ceron et al., J Infect. 2020

Seniors at greater risk

UK Long COVID study
Sudre et al medRxiv , 2020

- 4,182 COVID Symptom Study App symptomatic users:
- **COVID-19 symptoms > 4 weeks 13.3%**
- **8 weeks 4.5%**
- **>12 weeks 2.3%,**

- "Long COVID" **10% of 18-49 year olds** with COVID-19, **rising to 22% of over 70s.**
- Risk factors: high BMI
- **Younger women 50% more likely than younger men**

21 October 2020

New research identifies those most at risk from 'long COVID'

A new analysis by researchers at King's, using data from the COVID Symptom Study app, shows that one in 20 people with COVID-19 are likely to suffer symptoms for 8 weeks or more (so-called 'long COVID'), potentially adding up to many

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Comment

Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the Covid Symptoms Study App

Carole H. Sudre, Benjamin Murray, Thomas Varsavsky, Mark S. Graham, Rose S. Penfold, Ruth C. Bowyer, Joan Capdevila Pujol, Kerstin Klaser, Michela Antonelli, Liane S. Canas, Erika Mol, Marc Modat, M. Jorge Cardoso, Anna May, Sajaysurya Ganesh, Richard Davies, Long H Nguyen, David A. Drew, Christina M. Astley, Amit D. Joshi, Jordi Merino, Neli Tsereteli, Tove Fall, Maria F. Gomez, Emma L. Duncan, Cristina Menni, Frances M.K. Williams, Paul W. Franks, Andrew T. Chan, Jonathan Wolf,

About 1 in 5 adults older than 70, or 21.9%, who tested positive for coronavirus developed long Covid, compared with about 1 in 10 18- to 49-year-olds, the study found.
Women were more likely to suffer from long Covid than men -- at 14.9% of women compared to 9.5% of men -- but only in the younger age group.

These data precede Delta variant, anticipating increased rates with the higher viral load and inflammatory response during acute infection

Delta variant, vaccines and long COVID

- Great concern that long COVID risk is higher with Delta variant
- Vaccines only 40-60% effective in preventing infection, though very effective at preventing hospitalization
- But viral loads are higher, younger people are ill, and there is a concern from one and two month data that the Long COVID rates will be higher.

Treatment of Long COVID : General Principles

Acute CoVID impacts many organs systems – systematically review to assure that persistent symptoms are not a consequence of organ damage.

- Lung (spirometry in office, CT to follow)
- Heart – echo, if abnormal MRI for fibrosis
- Renal, Liver with blood screens
- Brain – consider CT or MRI if PE suggests focal brain issue

TREATMENT OF LONG COVID

- KNOWLEDGE IS RAPIDLY EVOLVING
- HERE I WILL PRESENT WHAT WE KNOW THAT IS UNIQUE TO COVID AND
- WHAT IS GLEANED FROM OUR KNOWLEDGE OF THE POST VIRAL ILLNESS, ME/CFS

Treatment of Long COVID : Smell and Taste

Acute COVID has sequalae unique to COVID infection – smell and taste Moat patients see tis improving and resolving in 2-4 months, however some patients suffer from prolonged abnormalities of absent or distorted smell and taste.

Testing smell in the office can be simple, using essential oils in a diagnostic set rose, lemon, clove and eucalyptus, commercial scratch and sniff tests are also available, e.g. Scent Check

Retraining of olfactory system is basically PT for smell – studies are underway, but patients are finding self help videos etc, using essential oils and visual association (e.g. strong rose smell and picture of rose)

Care to optimize nerve regeneration environment: antioxidants, adequate B vitamins , healthy fats in the diet, reduce inflammation in the nose (treat allergies with topicals and reduced exposures, treat gum disease)

Do the basics well: prevent and reduce mid- and long-term sequelae

- **Holistic approach to follow-up**: symptom and functional limitation assessments
  - symptom evaluation
  - standardized scales to assess: dyspnoea, functional disabilities
  - targeted physiologic testing based on symptoms: pulmonary function test, echocardiogram, CT scan, 6MWT, etc.

- **Multi-disciplinary care**: interventions based on diagnosis and/or functional limitations
  - self care
  - primary care including mental health services
  - specialists care as appropriate (pulmonary, neurologic, cardiac, etc),
  - rehabilitation.

- **Integrated into research agenda**
  - clinical characterization, impact of treatments on longer term outcomes.

IN ADDITION TO THE WHO GUIDELINES

STAY VERY TUNED IN – THINGS ARE CHANGING FAST, AS NEW KNOWLEDGE BEGINS TO HELP GUIDE THE HAND OF THE CLINICIANS

Covid-19 Patients Are Doing Their Own Research

To advance scientific knowledge of the disease, lay people are c
experiences

ILLUSTRATION: JOHN W. TOMAC

By Amy Dockser Marcus
Jan. 30, 2021 12:01 am ET

Event

COVID-19: A Primer Update From Treatment to Long Haulers

presented by American Academy of Anti-Aging Medicine

Saturday, July 17, 2021 9 AM - Sunday, July 18, 2021 6 PM America/New_York

EVENT INFO

Course Syllabus

Click HERE to view the

BMC

Blog Network About Blogs

long Covid

LATEST LONG COVID POSTS

The forgotten Covid-19 'survivors'

Dr. Emma Ladds, Dr. Sharon Taylor, Professor Trish Greenhalgh

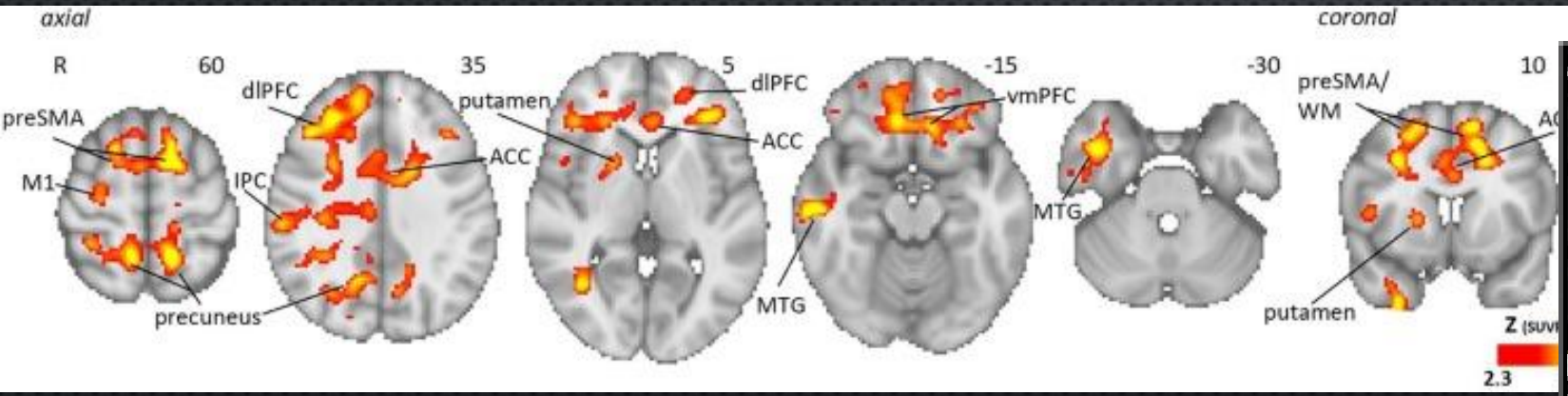
WHILE MANY OF THE MEDIATORS OF ILLNESS PERSISTENCE POST COVID ILLNESS ARE UNKNOWN, ME/CFS HAS HAD SEVERAL DECADES OF RESEARCH TO PROVIDE DATA INFORMING OUR UNDERSTANDING AND METHODOLOGY TO DISCOVER TARGETS FOR INTERVENTION, STUDIES TO DETERMINE DEGREE OF OVERLAP ARE UNDERWAY.

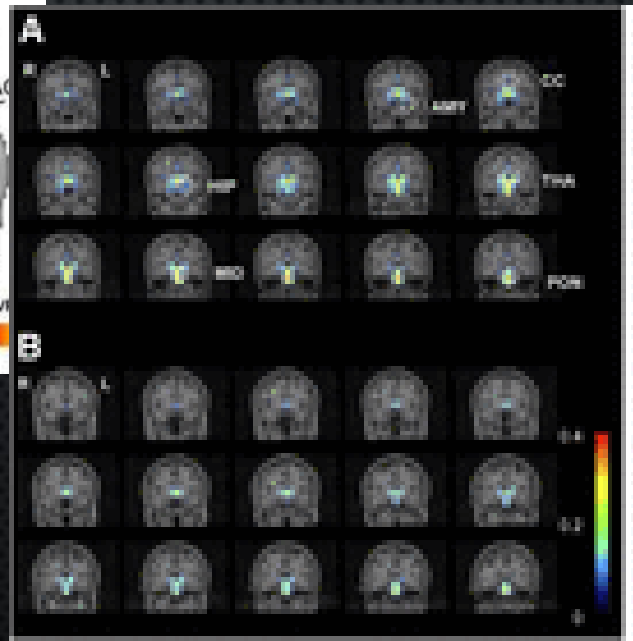
Building on what we know from ME/CFS

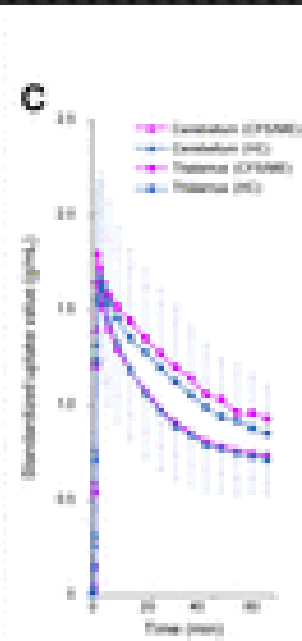
- Decades of work has resulted in an understanding of this complex illness and its underpinnings
- Multisystem illness, with mediators coming from brain, immune, hormone regulatory pathways as well as intracellular mechanisms (e.g. bioenergetics)
- The result has been put into a modeling system that has allowed our group to propose targeted interventions, taking into account the heterogeneity of the population.

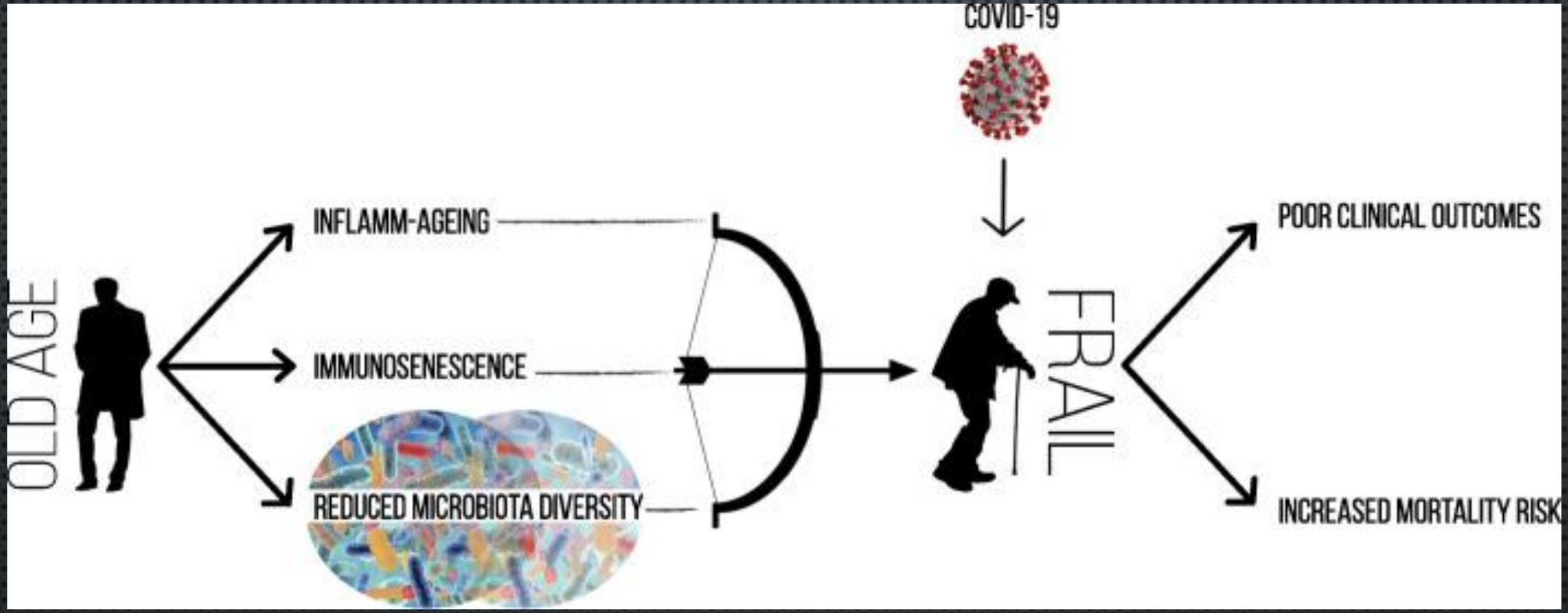
INFLAMMATION – BRAIN AND BODY

- **SYSTEMIC INFLAMMATION HAS BEEN DEMONSTRATED IN MULTIPLE STUDIES, WITH INFLAMMATORY CYTOKINES, ACTIVATED COMPLEMENT, IMMUNE ACTIVATION.**
- **NEUROIMAGING STUDIES AND SPINAL FLUID STUDIES ALSO DEMONSTRATE MARKERS OF INFLAMMATION IN THE BRAIN (Y. NAKATOMI, 2014)**









Hussien H, Nastasa A, Apetrii M, Nistor I, Petrovic M, Covic A. Different aspects of frailty and COVID-19: points to consider in the current pandemic and future ones. *BMC Geriatr*. 2021;21(1):389. Published 2021 Jun 27. doi:10.1186/s12877-021-02316-5

OXIDATIVE STRESS, MITOCHONDRIA, THE BRAIN

- Studies have shown depleted antioxidants in the body and in the brain (MRS studies – Shungu et al)
- In the brain oxidative stress promotes inflammation , finding antioxidants that cross the BBB is key to study designs –

NAC study underway at Cornell

HORMONES, HORMONE REGULATION AND ME/CFS

- - The neuroendocrine balance in ME/CFS shows a stable but "sick" balance, involving HPA, HPT, HPG axis,
- - Dynamic modeling increases the signal of the stress response and other neuroendocrine biomarkers, in the context of time, cascade of events and the role of the neuroendocrine system in perpetuating the homeostatic "sick" balance
- Computational models include the neuroendocrine features in predicting treatments and differ by age and gender as well as comorbid anxiety features.

PUTTING IT ALL TOGETHER : HOMEOSTASIS

- This is our team's moonshot vision initiated 10 years ago and the focus of a series of DoD, NIH RO1's and VA Merit awards
- Using human studies of men and women with ME/CFS and also Gulf War illness, our studies explore the relationship of the immune, neuroendocrine, and autonomic nervous system, and its relationship to health, illness and relapse resulted in sophisticated models of illness persistence. The models are comprehensive. They predicted interventions that have successfully reset homeostatic balance in animal models. As a result two phase 1 studies are underway in GWI and a phase 2 study funded on the strength of these preliminary studies. A ME/CFS phase 1 study is about to be initiated,

Learning from ME/CFS : Treating the Mediators of Persistence

- Inflammation (brain and body). Treatments need to cross BBB (e.g. low dose naltrexone, nanocurcumin, omega 3)
- Poor antiviral function with reduced cytotoxic function, chronic immune activation (bioenergetic approaches, antivirals, control allergens, toxins exposures)
- Mast cell activation - mast cell stabilizers, nonsedating antihistamines
- Evidence of viral reactivation (eg HHV6, EBV, Coxsackie B) – perhaps antivirals

Learning from ME/CFS : Treating the Mediators of Persistence

- Hypercholinergic state with dysautonomia, low blood volume – electrolyte solutions, perhaps low dose beta blockers, midodrine (alpha1 agonist)
- Dysregulation of hypothalamic and pituitary function – deep endocrine eval
- Poor sleep quality – sleep study to r/u upper airway resistance, avoid alpha wave trappers (sedatives) consider low dose TCA (eg doxepin 5-10mg) or melatonin if need be

Learning from ME/CFS : Treating the Mediators of Persistence

- Bioenergetics (depleted antioxidants, reduced mitochondrial function). Treatments need to cross the BBB (eg NAC, intranasal glutathione, others)

Implications for treatment - NMH

"Pipes and a pump", wired by the autonomic nervous system

- Fill the space – increase plasma volume (electrolyte or fludrocortisone)
- Regulate the pump - beta blockers
- Compress the space - alpha 1 agonists (e.g. midodrine), anti-phlebitic stockings, core muscle strengthening

Dysautonomia

- **Recumbent exercise and Isometric exercises.** Simple physical isometric exercises .
- **Compression garments.**
- **Pharmacological treatment**
- If POTS features are present, norepinephrine reuptake inhibitors such as duloxetine, nortryptiline and tapentadol should be discontinued if possible.
- Fludrocortisone, a fluid expander, can be used . Monitoring should take place for fluid retention and hypokalaemia., monitor with a 4 week check and quarterly electrolytes
- Midodrine, a sympathomimetic a-1-agonist, increases vasoconstriction and venous return to the heart. Supine hypertension is possible as is Urinary retention on men, scalp itch is a common side effect
- For prominent hyperadrenergic symptoms caused by the catecholamine surge on standing, clonidine and methyldopa may alleviate symptoms. Similarly, propranolol can attenuate palpitations and tachycardia. However, none of these agents is well tolerated.

- Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, Lim PB. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. Clin Med (Lond). 2021 Jan;21(1):e63-e67. doi: 10.7861/clinmed.2020-0896. Epub 2020 Nov 26. PMID: 33243837; PMCID: PMC7850225.

SLEEP: TREATMENT

- Re-establish circadian rhythm
- Consider CPAP for upper airway dysfunction

Conditioned response to bed - avoid bed for resting, reading, use bed for sleeping. Establish "bedtime".

- Avoid short acting hypnotics except in true insomnia (alpha trappers)
- tricyclics, doxepan are longer acting, and don't trap in alpha wave
- mirtazapine (Remeron), gamma hydroxybutyrate, (Xyrem) act as SWS inducers, ?melatonin,
- eszopiclone(Lunesta), zaleplon (Sonata), and zolpidem (Ambien) sleep neutral
- Sleep studies very helpful as many as 50% of profoundly fatigued people have sleep apnea

Pain and Sleep

- Clinical dogma "restorative sleep is key to improvement"
- The trials in FM report pain improvement with sleep restoration and vice versa
- Experience has taught us that this is not always generalizable – it would be helpful if there were studies in Long COVID

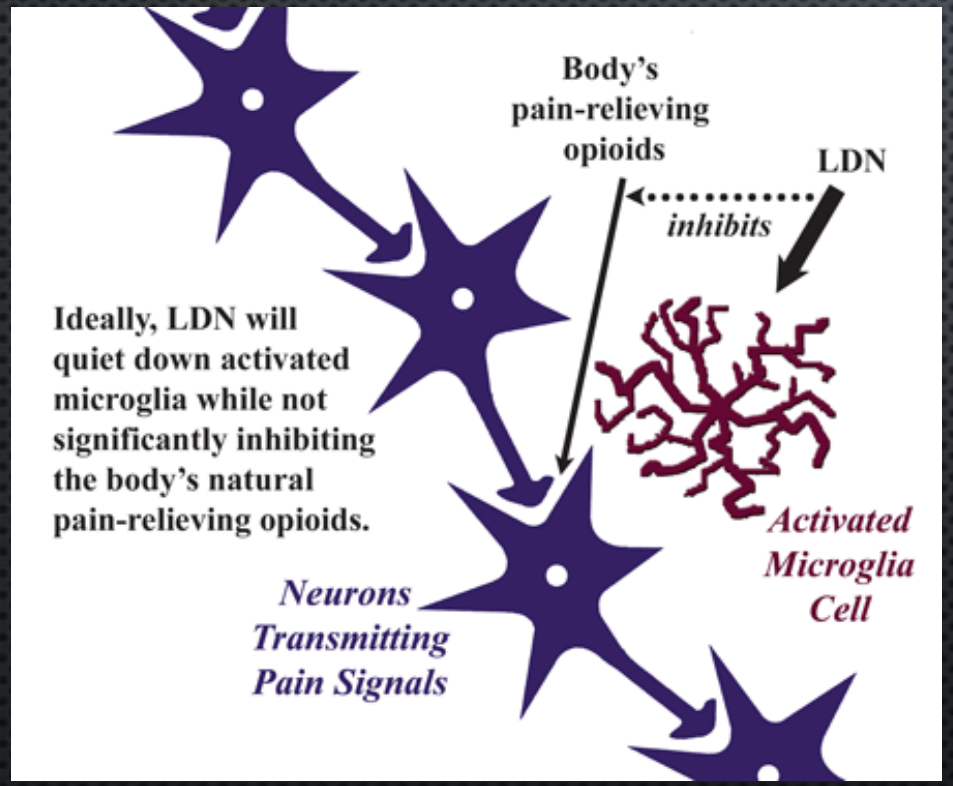
Pain

In Fibromyalgia patients and FM subset of GWI or CFS there are 3 labeled pain medications and 1 pipeline sleep medication

- Pregabulin (Lyrica)
- Duloxetine (Cymbalta)
- Milnacipran (Savella)
- Opiates, alcohol increase neuroinflammation and reinforce central pain processing upregulation

- Low dose naltrexone

LOW DOSE NALTREXONE (OFF LABEL USE)



Compounded
1.5 mg qhs for 4 weeks then
3.0 mg for 4 weeks
Then 4.5 mg fpr 4 weeks

Side effects: enhanced REM sleep , vivid dreams can occur – if so switch to am use


ISTOCKPHOTO.COM/ELIZA SNOW
ISTOCKPHOTO.COM/CORACHROS
ISTOCKPHOTO.COM/TRISTA WEIBELL

While you are waiting for the answers what should you do

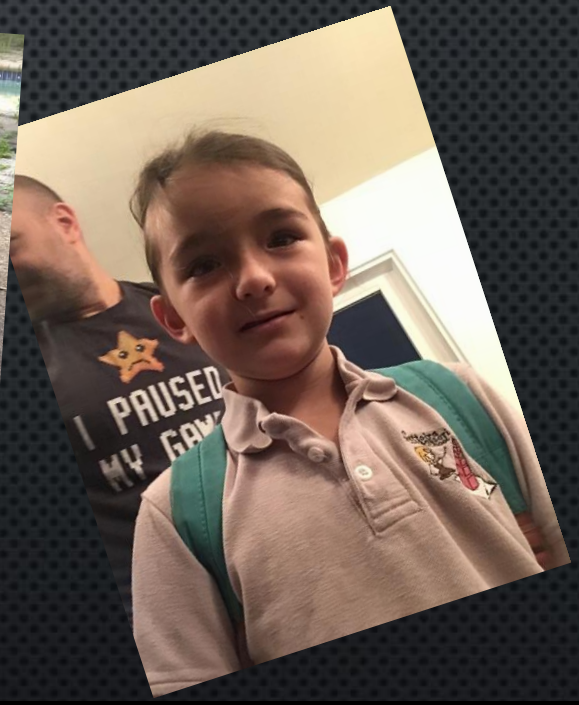
- After you make sure your lungs, heart and brain have no structural damage then you should learn from the ME CFS experience and use these resources:
- Clinical guidelines for ME/CFS website: https://mecfsclinicianscoalition.org/
- Patients should know about this patient blog site : https://www.healthrising.org/
- And don't forget us: https://www.nova.edu/nim/index.html

The most significant thing ME/CFS can teach doctors about long COVID is to "be humble," he added. "What it [ME/CFS] has taught us is that there are limits to medical knowledge and to medical practice," he said.

Dr. Avindra Nath, clinical director of the National Institute of Neurological Disorders and Stroke

THANK YOU

- QUESTIONS?



Summer interns Talia and Callie

COVID-UPP OVERVIEW

Part 1 (N=700)

Aim 1:

- Among a large, racially/ethnically diverse population who tested positive for COVID-19 and who report at least two ME/CFS symptoms (per the ME/CFS SI grid) describe the proportion, frequency and severity of ME/CFS symptoms at three to four months post infection.

- **Aim 2:**
- Among a large, racially/ethnically diverse population who tested positive for COVID-19 and who report at least two ME/CFS symptoms, assess the rate of developing ME/CFS overall, and by race/ethnicity (Non-Hispanic Black, Non-Hispanic White, Hispanic) over time.

  Aim 2a: Among a large, racially/ethnically diverse population who tested positive for COVID-19 and who continue to report being unrecovered from COVID-19 over time, describe the trajectory of ME/CFS symptoms and associations with developing ME/CFS.

Part 2 (N=200)

Aim 3:

- In a subgroup of the survey population, perform clinical and biologic evaluations to better describe the presentation and mediators of illness, and compare these findings with two historical cohorts of ME/CFS (CDC MCAM study and NSU studies of ME/CFS)