

“Post COVID neurological sequelae”

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No disclosures

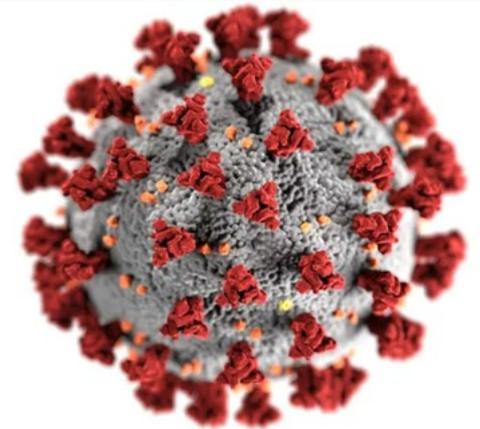
Lecture Outline

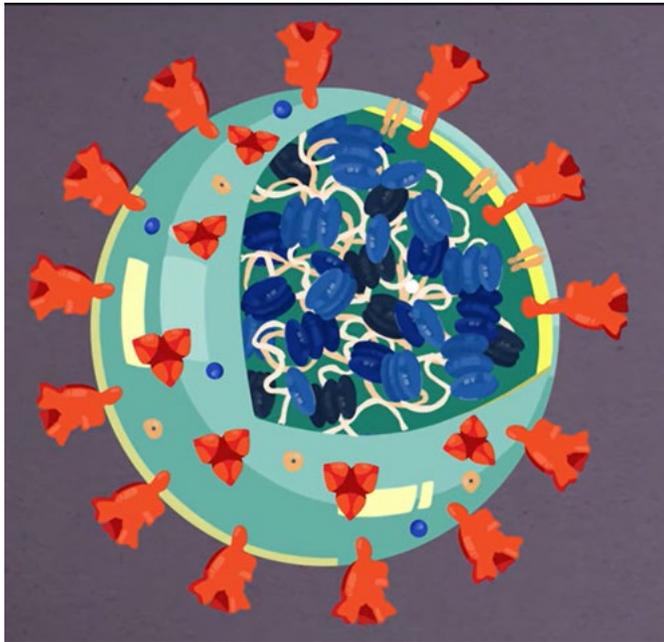
- Define post COVID syndrome
- Neurological complications of “Long COVID “
- Diagnosis ,treatment and prognosis of “Long COVID “
- Our role moving forward

SARS-CoV-2: severe acute respiratory syndrome
corona virus 2

COVID -19: corona virus disease 2019

1st detected in Wuhan, China and named by the
WHO 2/11/20





Viral Envelope – waxy barrier providing protection and anchors structures necessary to infect a cell

Spike Proteins – give the virus its crown-like appearance and the “corona” moniker. They act as grappling hooks allowing the virus to latch onto host cells and crack them open for infection

RNA – a single stranded genetic blueprint that acts as a molecular message allowing production of other elements of the virus

Nucleoproteins – bound to the RNA and help give the virus its structure and enable it to replicate

Proposed nomenclature

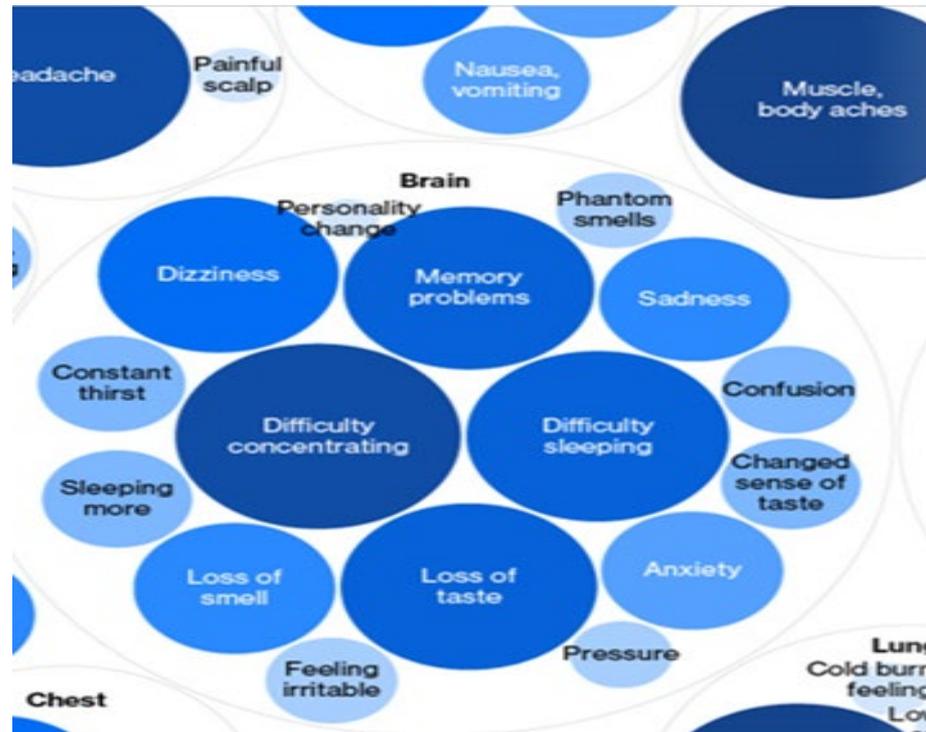
Table 1. Proposed descriptions of long COVID.

Reference	Terms	Description
[4] [5,6,7]	Long COVID Long-hauler COVID-19 Long-COVID Chronic COVID syndrome	Long-term COVID-19 illness that is cyclical, progressive, and multiphasic. Multi-organ symptoms that persist for months after acute COVID-19.
[8]	Long-haul COVID Long-tail COVID	Symptoms lasting for > 100 days.
[9,10] [11,12,13]	Long COVID Late sequelae of SARS-CoV-2 infection Long-haulers Long-COVID	Symptoms lasting for > 2 months. Symptoms lasting for > 4 weeks after the initial infection or diagnosis.
[14]	Post-acute COVID-19 syndrome	Symptoms lasting for > 4 weeks after the first symptom onset.
[15]	Acute post-COVID symptoms Long post-COVID symptoms Persistent post-COVID symptoms	Symptoms lasting for 5-12 weeks. Symptoms lasting for 12-24 weeks. Symptoms lasting for > 24 weeks.
[16, 17,7]	Post-acute COVID-19 On-going symptomatic COVID-19 Chronic COVID-19 Long COVID Post-COVID-19 syndrome	Symptoms lasting for 1-3 months from the first symptom onset. Symptoms lasting for > 3 months from the first symptom onset.

Post COVID syndrome

- Defined as by World Health Organization as symptoms that occur 3 months from onset of COVID or
- Symptoms that occur at least 2 months and not explained by any other diagnosis
- Symptoms of fatigue ,shortness of breath and cognitive dysfunction
- Symptoms impacting everyday function
- Fluctuating or relapse noted over time

Post COVID syndrome



Post COVID syndrome

Epidemiology

- 170 million cases worldwide ,45 million in US
- Recent study showed that 54 % of hospitalized COVID patients had one of the PACS symptoms for at least 6 months
- 35-40% of non hospitalized patients had symptoms 2-4 months later
- 10-30% with long COVID never hospitalized
- Males more likely to get COVID and die
- Females if you survive you will get long COVID



Post COVID syndrome

Epidemiology

- Neurologic manifestations occurred equally in men and women
- African American compared to Caucasian patients had higher odds of developing neurologic manifestations (odds ratio [OR], 1.26; 1.09–1.46; $p = 0.002$)
- South Asian patients had lower odds for developing neurologic manifestations (OR, 0.33; 0.18–0.61; $p < 0.001$)

Post COVID syndrome

Issues with Long-COVID

- Some patients acquired COVID and were asymptomatic (and likely not tested), so clinically relevant symptoms may not/ will not be recognized.
- Some patients received a false negative test (test done too early or too late) and have residual symptoms unrecognized as COVID-related.
- At first, doctors dismissed patient concerns as symptoms related to mental health, such as anxiety or stress, in a phenomenon called “medical gaslighting”



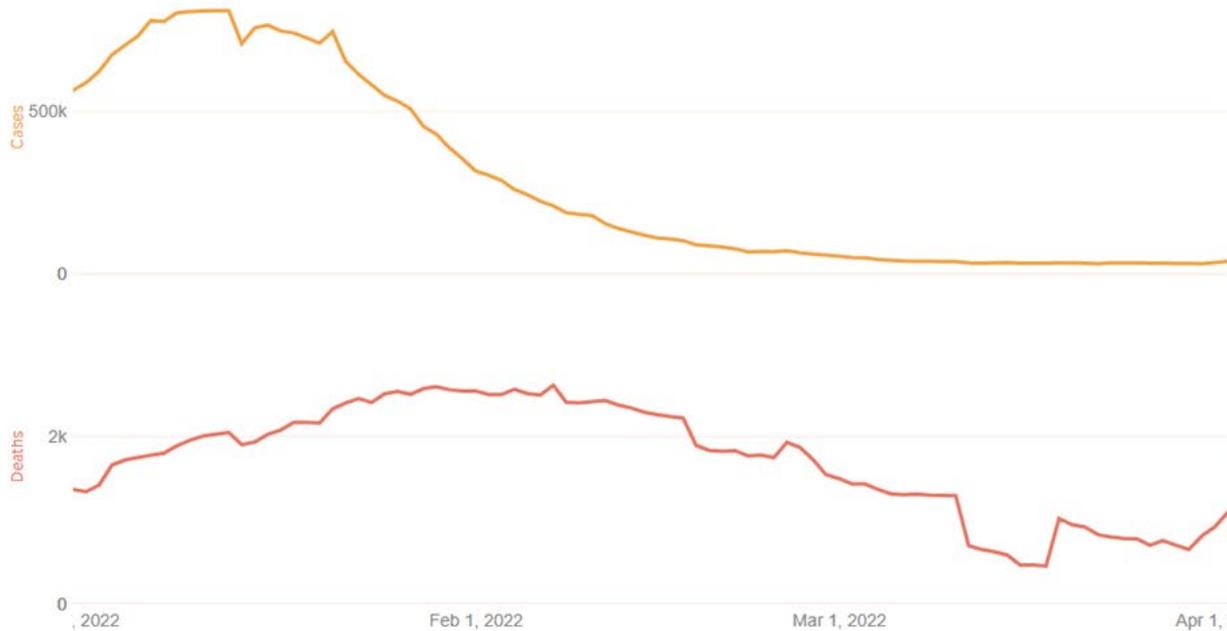
Photo from: Long Covid: These Are The Symptoms And Treatments

Yong et al. (2020); Maxwell et al. (2020); Raveendran et al. (2021); Rubin (2020)



All Time

Last 90 Days



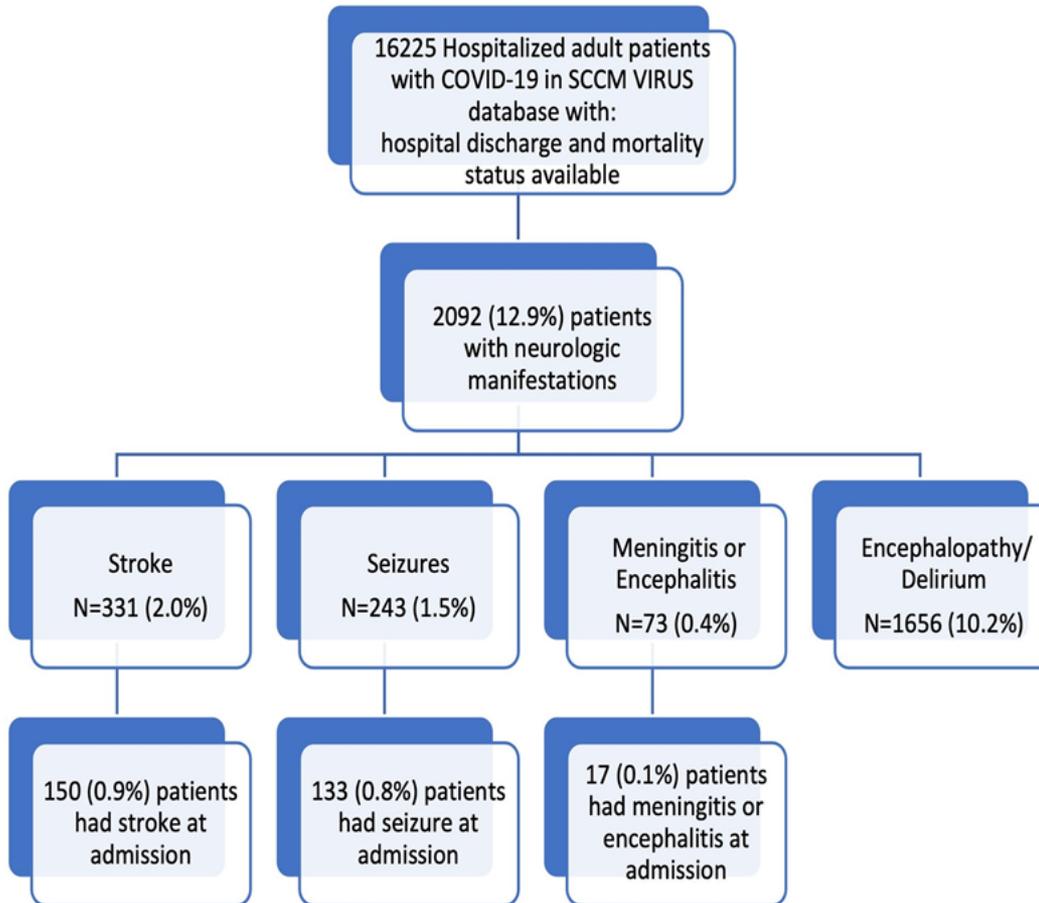
Choose datasets to compare 7-day average timelines:

- Cases
- Deaths
- Hospitalizations
- Test Positivity

You must choose at least two datasets.

Data Sources: Cases and deaths data from JHU CSSE; testing and vaccine data from JHU CCI; and hospitalization data from the U.S. Department of Health and Human Services.

Neurological Complications



Neurologic Manifestations of Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Hospitalized Patients During the First Year of the COVID-19 Pandemic
Cervantes-Arslanian, Anna et al .
Critical Care Explorations April 2022

Neurological Complications

- Patients with serious neurologic manifestations of COVID-19 were older with median (interquartile range) age 72 years (61.0–81.0 yr) versus 61 years (48.0–72.0 yr) and had higher prevalence of chronic medical conditions, including vascular risk factors
- Adjusting for age, sex, and time since the onset of the pandemic, serious neurologic manifestations were associated with more severe disease (odds ratio [OR], 1.49; $p < 0.001$)

Neurological complications

- Patients with neurologic manifestations were more likely to be admitted to the ICU (OR, 1.45; $p < 0.001$) and require critical care interventions (extracorporeal membrane oxygenation: OR, 1.78; $p = 0.009$ and renal replacement therapy: OR, 1.99; $p < 0.001$)
- Hospital, ICU, and 28-day mortality for patients with neurologic manifestations was higher (OR, 1.51, 1.37, and 1.58; $p < 0.001$), and patients had fewer ICU-free, hospital-free, and ventilator-free days

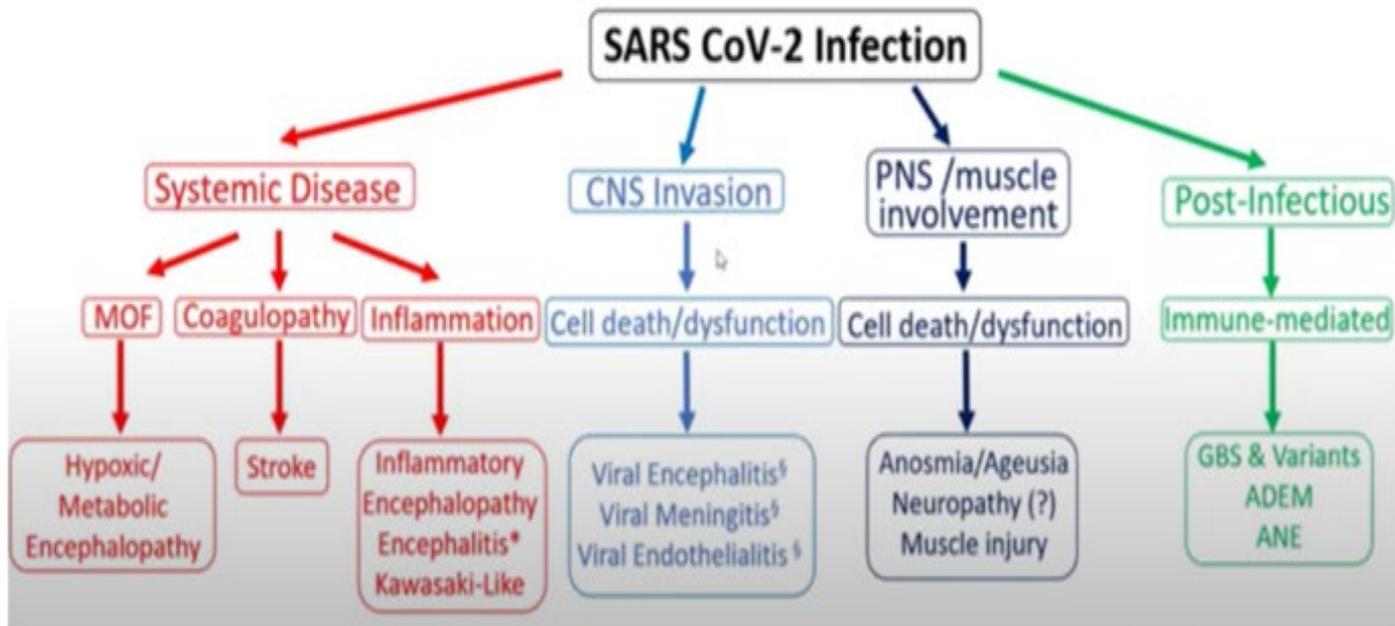
Neurologic Manifestations of Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Hospitalized Patients During the First Year of the COVID-19 Pandemic Cervantes-Arslanian, Anna et al . Critical Care Explorations April 2022

Neurological complications

- Meningitis/encephalitis
- Stroke
- Anosmia/ageusia
- AIDP/Guillian Barre Syndrome
- Acute disseminated encephalomyelitis
- Seizures

Neurological complications

SARS-CoV-2 Neuropathogenesis: multifactorial Koralnik and Tyler Ann Neurol 2020



Neurological complications

- Patients with strokes were on average older with the majority having underlying vascular risk factors, with greatest risk in those with a history of prior stroke and/or dementia
- This suggests exacerbation of underlying cardiovascular and cerebrovascular disease as a main culprit etiology

Neurological Complications

- However, many series reported younger average age in patients with stroke and a meta-analysis has shown that while strokes on average occurred in older COVID-19 infected patients, patients with COVID-19 infection and stroke were typically younger than uninfected patients with stroke

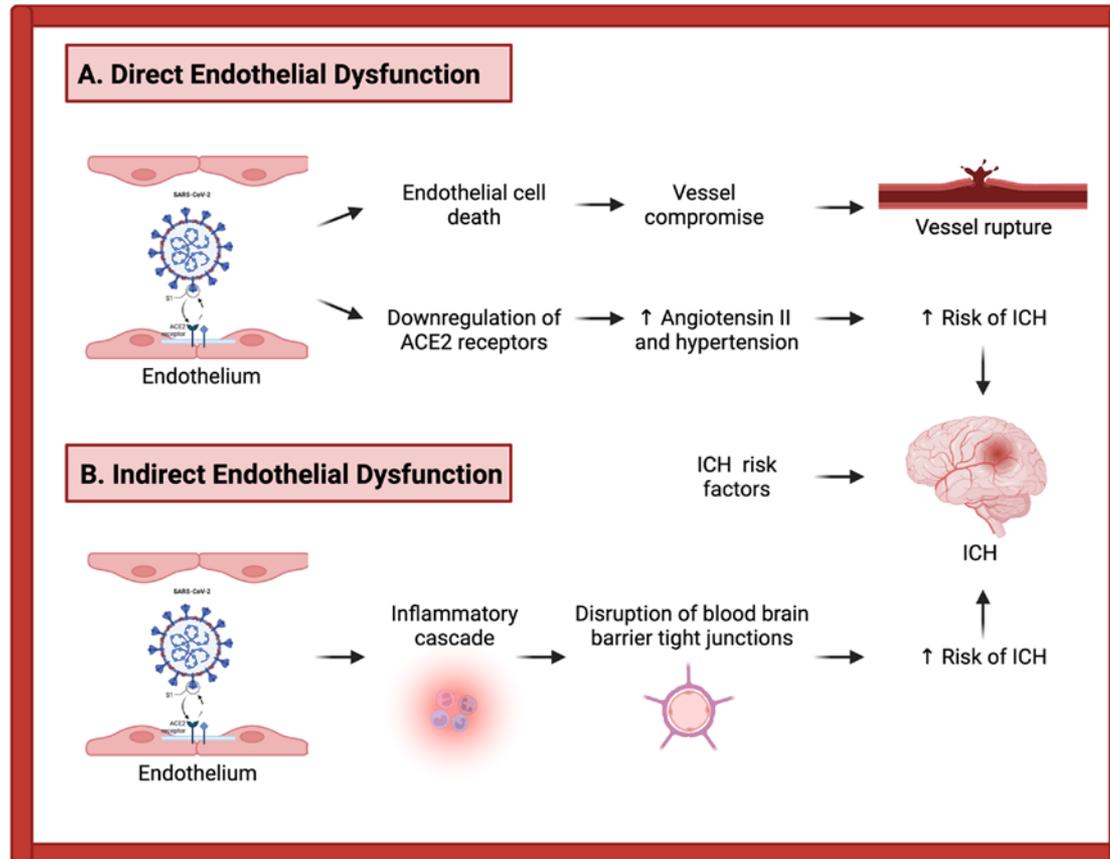


Neurological Complications

- It is notable that 13% of patients in certain cohorts with stroke had no identifiable vascular risk factors
- Other early studies similarly noted an absence of typical risk factors in some patients
- This suggests that stroke in COVID-19 may also occur due to less common mechanisms such as virally mediated hypercoagulability, cardiac-specific effects, cerebrovascular arteriopathy, or endothelitis

Neurological Complications

- Hemorrhagic strokes



Neurological complications

Neurological Symptoms--Brain Fog

- ▶ Most common neurological symptom
- ▶ Issues with short-term memory, concentration and word-finding/speech difficulty
- ▶ No clear correlation with severity of COVID infection, age or comorbidities
- ▶ Symptoms often fluctuate, "good and bad days"
 - Fluctuations often correlate with other symptoms like fatigue and dysautonomia
- ▶ Impact on life varies: some able to still work, others on disability
- ▶ Sleep: many patients with poor sleep
- ▶ Mood: many patients experiencing depression, anxiety and/or PTSD

Neurological Complications

Neurological Symptoms--Headaches, Paresthesias and Dysautonomia

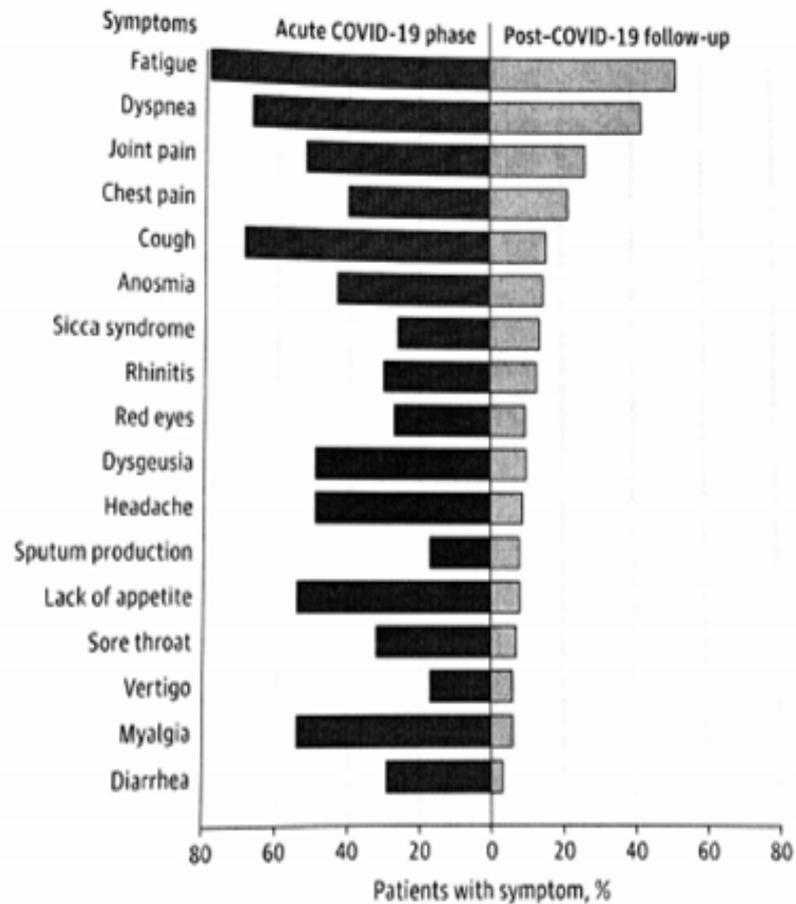
- ▶ Headaches
 - Often describes as constant pressure that can fluctuate in severity
 - May have migraine symptoms or not
 - Many don't have a history of headaches

- ▶ Paresthesias
 - Tingling, numbness and/or burning sensation
 - May be focal, diffuse, alternating in locations
 - Sometimes more in distal extremities (stocking-glove distribution)

- ▶ Dysautonomia
 - Fluctuating blood pressure and heart rate
 - Lightheadedness, palpitations, GI disturbances

Most patients have multiple chief complaints. Rare to have someone coming in for only one issue

Figure. COVID-19-Related Symptoms



The figure shows percentages of patients presenting with specific coronavirus disease 2019 (COVID-19)-related symptoms during the acute phase of the disease (left) and at the time of the follow-up visit (right).

Carfi, A. Persistent Symptoms in patients after Acute COVID 19. JAMA. 324(2020)

Diagnosis

Workup--often aimed to look for contributing factors

- ▶ Bloodwork
 - TSH, Vitamin B12 and Vitamin D
 - HIV, RPR, thiamine, folate (if severe cognitive deterioration)
 - Hemoglobin A1c if neuropathy

- ▶ Imaging- MRI Brain (or CT Head)

Consider Imaging:	Can Consider Holding Imaging:
<ul style="list-style-type: none">• Moderate-Severe COVID• Over 50 years of age• Medical comorbidities/risk factors• Impact on job or iADLs• Focal neurological deficits or symptoms	<ul style="list-style-type: none">• Not hospitalized/no complications with COVID• Less than 50 years of age• Otherwise healthy• Correlation with other symptoms, has "good days"

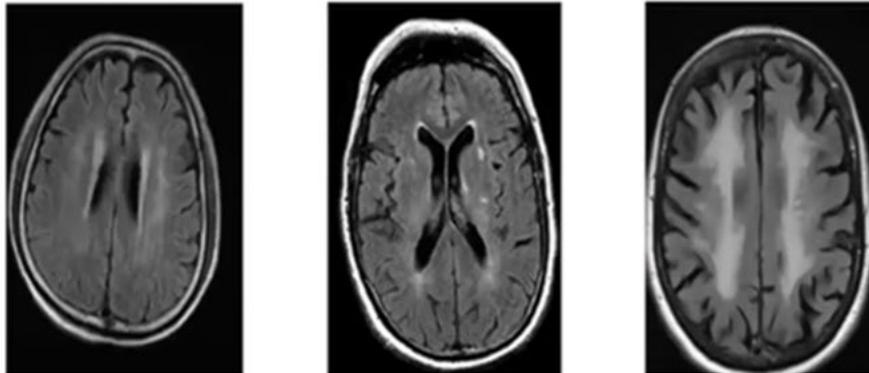
- ▶ Neuropsychological Testing
 - Can be helpful in highlighting if/what deficits present as well as potential contributing factors

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Diagnosis

Neuroimaging: typical findings

- ▶ Not seeing large inflammatory/infectious appearing lesions
- ▶ Not seeing many strokes, including lacunar strokes
- ▶ White matter changes (i.e., microvascular ischemic changes)
 - Very common imaging finding regardless of COVID
 - Occurs with age, vascular risk factors, migraines
 - Unless severe, often not considered clinically relevant
 - Caution in attributing to COVID without comparison imaging, or, if more severe than expected for age



Diagnosis

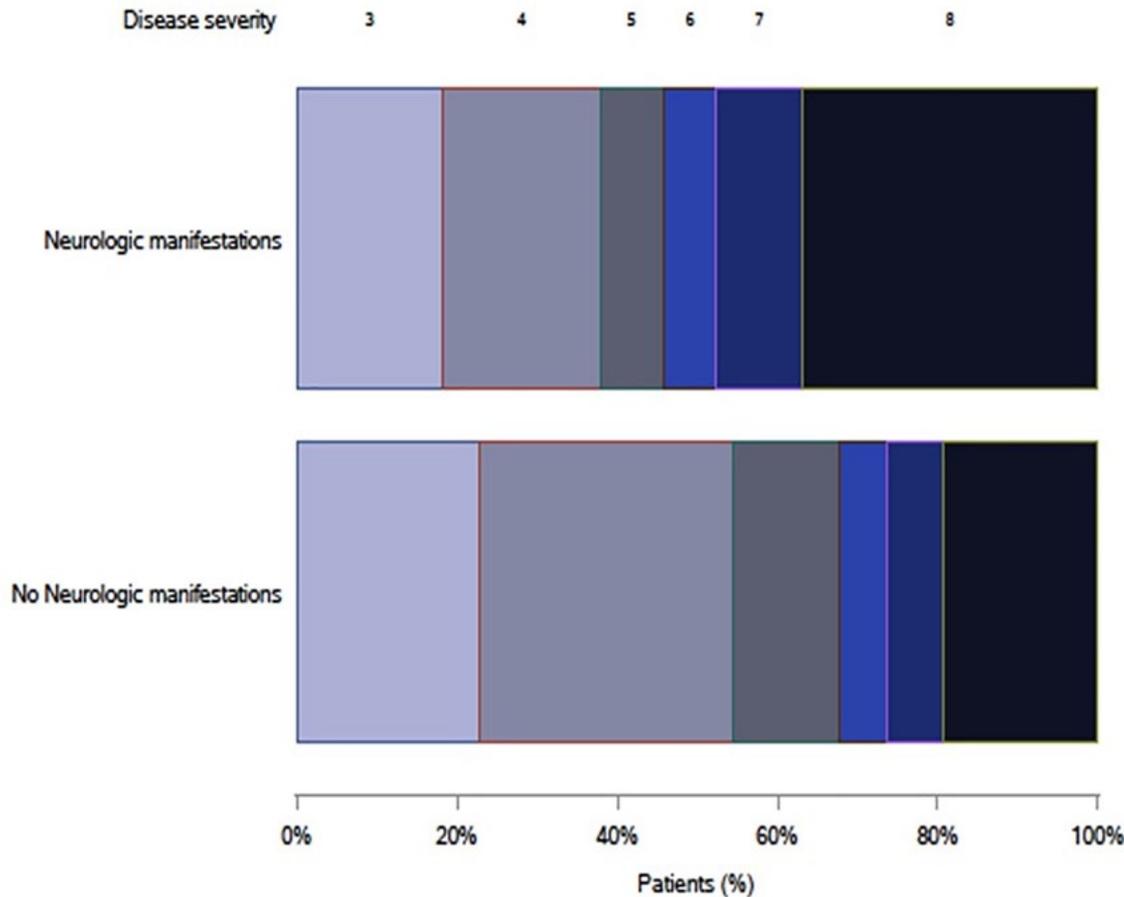
What may be occurring?

- ▶ Damage to central nervous system (CNS)?
 - Lack of evidence to support/refute
 - Unlikely widespread CNS infection. Role of vasculature?

- ▶ Peripheral nervous system may be affected
 - Much more vulnerable to systemic insults than central nervous system
 - Presence of small fiber neuropathy?
 - Small fiber neuropathy leading to dysautonomia?

- ▶ Other, possibilities:
 - Postural orthostatic tachycardia syndrome (POTS)
 - Hyperadrenergic POTS relating to excessive catecholamines?
 - Myalgic encephalomyelitis/chronic fatigue syndrome (MECFS) like process?

Prognosis and Treatment



Outcomes between patients with and without neurologic manifestations according to the World Health Organization's ordinal scale for disease severity. Disease severity score of 3 indicates hospitalized with no supplemental oxygen; 4—requiring oxygen by mask or nasal prongs; 5—required noninvasive ventilation or high-flow oxygen support; 6—intubation and mechanical ventilation; 7—ventilation with additional organ support (vasopressors, renal replacement therapy, extracorporeal membrane oxygenation) and a disease severity score of 8 indicates death.

Prognosis and Treatment

Conclusion

- ▶ Many neurological symptoms present in post-COVID patients
- ▶ Many symptoms may correlate, important to get broad history
- ▶ So far, diagnostic workup is not providing much information
 - Likely okay to do less testing, unless red-flag symptoms present
 - Important to not over-interpret things like imaging
- ▶ Treatment is supportive and symptomatic
 - We don't have medications to "cure" neurological damage
- ▶ Multi-disciplinary approach with post-COVID experience is critical
- ▶ We don't know what is causing symptoms, but that does not mean this is not real.
- ▶ Reassurance. Patients can/do get better.

Non-hospitalized Covid-19 “long haulers” study

- Prospective study of **first 100 consecutive patients** presenting to the Neuro-Covid-19 clinic at Northwestern Memorial Hospital
- May-November 2020
 - May-June: televisits only
 - July-November: in-person and televisits
- Physician referral or + SARS-CoV-2 test **not** requested
 - 50 SARS-CoV-2+ and 50 SARS-CoV-2-
- Inclusion criteria:
 - IDSA clinical symptoms of Covid-19 starting February 2020 or later
 - **No hospitalization for pneumonia or hypoxemia**
 - Neurologic symptoms persisting > 6 weeks from symptom onset



Long Haulers study

- Headache
- Dizziness
- Increase/decrease heart rate/blood pressure
- GI disturbances
- Muscle/joint aches
- Fatigue
- Sleep disturbance
- Brain fog (word-finding difficulties, memory impairment, problems with focus/attention)

Long Haulers conclusion:

- Prominent and persistent **brain fog and fatigue** in “ long haulers”
- Impaired quality of life in areas of **Cognition and Fatigue**
- Impaired **Attention and Working Memory** in SARS-CoV-2 positive patients
- **Diagnostic dilemma** in SARS-CoV-2 negative patients
- **High female:male ratio** and prevalence of pre-existing auto-immune diseases c/w post infectious, auto-immune etiology of long Covid-19
- Time from onset not good predictor of recovery: **individual trajectory**
- Millions of people affected in the world: **significant impact on workforce**

Cases

- Of note Mount Siani Post COVID 19 clinic reported 1/3 of 300 outpatient referrals to neurology cardiology and/or pulmonary
- Following post COVID cases are from our neurology clinic outpatient

Cases

72 Y/o woman admitted to SARH on 1/9/22 with ambulatory difficulty and confusion and was positive for COVID-19. She remained weak on the left side. She was now at Ability Pathways (Gibbs) with hx of developmental delay (mild). She had remained less mobile and much less verbal prior to which she was independent. She was COVID+ on 1/9/22 and 1/17/21 on apixaban.

Neurological exam aphasic with left sided plegia

Diagnostic test

MRI (1/10/22): small focus of acute/subacute infarct in R frontal lobe at superior margin of right insular cortex. EF per Echo was 60-65% (1/22')

Treatment plan :encephalopathy worse than expected from stroke ? COVID related started Provigil for stroke continue Lipitor and apixaban ,U/S carotids

Cases

68 y/o woman known hx of OSA ,HTN on CPAP was + for COVID with dyspnea, cough, fever/chills in Dec 2020. She had since noted more headaches, fatigue, confusion/memory difficulty. Her headaches persisted near daily that was bifrontal maximal or on either temporal region that was throbbing with light sensitivity.

Exam :BMI: 30.66 Pulse rate: 67 / minute BP sitting: 137 / 87 (right arm)

Neurological exam : non focal

Diagnostics:

MOCA 11-8-21: 24/30. 8/10 depression

MOCA 3-25-2021: 17/30; DEPRESSION: 10/10; MCI >90%

BRAIN MRI 3-17-2021: UNREMARKABLE

EEG 5-4-2021: Drowsiness and stage II sleep is WNL No focal dysfunction or epileptiform activity is identified

Treatment plan : sleep study ,CPAP and amitriptyline for headaches improved symptoms

Cases

67 y/o woman was a resident of a long term facility and had a hx of seizures and dementia. She was non verbal and non-ambulatory. As per her RN, she seemed to have declined significantly and was much less awake. She was somnolent during the daytime. She had frequent coughing during meals and required a G-tube. She was COVID + in Jan 2022 after which this decline was most noticeable. Her last seizure was in May 2021. She is still taking Levetiracetam 100mg/ml 6ml BID, Oxcarbamazepine 300mg BID, Vimpat 200mg BID.

Neurological exam Weight: 137 pounds BMI: 20.23 Pulse rate: 82 / minute BP sitting: 132 / 79 (right arm) diffuse weakness ,wheel chair bound non verbal

Diagnostic tests :EEG and CT head non remarkable

Treatment Plan :Substantial post-COVID cognitive declined and reduced arousability, the latter in part maybe due to her disturbed nocturnal sleep ,continue physical therapy and

Cases

24 y/o man had symptoms of imbalance as of late Aug 2021. At that time, he was drinking heavier on the weekends but even after stopping it he felt his sense of vague oddness in the head persisted. He eventually noted a sense that events or earlier parts of the day were much more distant. He had noted difficulty socialization and communicating difficulty with others where he seemed to not comprehend others. He had contracted COVID in Dec 2020 but no lingering effects.

Vital BP 131/95

Neurological exam Mental Status: A & O x 3. Cranial nerves: grossly Normal bilaterally. Motor Strength: Moving all extremities. Reflexes: symmetric. Sensory: intact to light touch. Coordination: finger to nose is symmetrically intact. Gait: non-ataxic.

Diagnostic tests

MRI Brain (12/14/21): R temporal choroidal fissure cyst 7mm

TSH ,B12 folate ,ANA ,Trepomona Ab WNL

Cases

62 y/o woman RN at PVMC and had COVID in 2020 and since then had become forgetful. She would forget the calls she would make to the doctors. She would lose her items. She had no issues driving but might forget where she parked. She c/o daily headaches worse since COVID that remained mild but more persistent

Vitals BP 128/65

Neurological exam Mental Status: A & O x 3. Cranial nerves: grossly Normal bilaterally. Motor Strength: Moving all extremities. Reflexes: symmetric. Sensory: intact to light touch. Coordination: finger to nose is symmetrically intact. Gait: non-ataxic.

Diagnostic test :

MOCA 19/30

EEG and CT head unremarkable

Treatment plan :post COVID cognitive impairment ,headache treatment with amitriptyline and encourage exercise

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© Z. Nasreddine MD Administered by: Laronda HHH		www.mocatest.org Normal ≥ 26 / 30		TOTAL 19/30 Add 1 point if ≤ 12 yr edu																									

Noted moderate impaired visuospatial /executive function
 Mild impaired naming and attention
 Moderate in language and delayed recall

Cases

- As with other illnesses especially when hospitalizations occur, we often see worsening cognitive function
- Recovery from surgeries, ICU stays, viral illnesses can take weeks to months
- COVID is no different and exacerbation of underlying dementia is seen with the infection and with the hospitalizations
- There is an increased risk of delirium in patients with underlying cognitive disorders
- A work up including neurologic exam, cognitive assessment, labs and imaging may be indicated as well as a review of meds and eval for underlying mood disorders and sleep disorders

Neuropsychiatric sequelae

- Depression, anxiety, PTSD, memory loss, fatigue
- 1/3 of COVID survivors received a neuropsychiatric diagnosis within 6 months after first symptom onset. (This is 44% more common than influenza survivors).
- ICU survivors 56% more likely to develop a neuropsychiatric disorder compared to non ICU-survivors
- Multiple psychiatric symptoms stemming from encephalopathy or encephalitis with primary psychiatric diagnosis found more commonly in younger patients
- Delirium caused by encephalitis
 - Occurred in 20-30% of hospitalized patients with severe cases
 - Long-term neurological problems make delirium more likely and is a strong predictor of other cognitive impairments in older adults.
- Acquired focal or multifocal peripheral nerve injury noticed in patients who received ventilation for COVID

Mao, Jin, & Wang (2020); Varatharaj et al. (2020); Malik et al. (2020); Nizar et al. (2020); Woodruff et al. (2020); Mucha et al. (2020)

Pathological inflammation

- T-cells dysfunction may promote long COVID pathophysiology similarly in autoimmune diseases.
- SARS-CoV-2 could make antigen-presenting cells present antigens to autoreactive T-cells in the process (bystander activation).
- SARS-CoV-2 nucleic acids and proteins in the small intestines were discovered in 50% of asymptomatic cases at a 4-month post-disease onset.
- Viral persistence in the body is possible which may induce some level of immune activation contributing to Long COVID.

Role moving forward

- Always make sure to rule out other mental health disorders like
- Post traumatic stress disorder ,depression ,anxiety and sleep disorders
- Chronic fatigue syndrome /myalgic encephalomyelitis like
- Fibromyalgia ,post concussive syndrome ,mild cognitive impairment ,post chemotherapy cognitive changes

Role Moving Forward

- COVID 19 recovery clinic
- Comprehensive physical ,cognitive and psychological assessment
- Appropriate referral to subspeciality clinics like cardiology ,pulmonary ,ENT ,neurology ,psychiatry ,rehab
- Young patients need primary care doctors
- Lab work ,imaging and diagnostic tests
- Follow up with physical ,occupational and cognitive therapy

Long Term Health Effects of other Corona Virus Infections

A study was performed on the long term effects of severe acute respiratory syndrome (SARS), the coronavirus that emerged in 2003

- This study showed there was **persistent and significant impairment of exercise capacity** and health status in survivors of SARS over 24 months. Health workers who had SARS experienced even more marked adverse impact¹
- Another study, revealed that **40%** of people recovering from SARS still had chronic fatigue symptoms 3.5 years after being diagnosed²

¹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7192220/>

² <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/415378>

The Patient Led Collaborative

- A self-organized group of individuals with PASC who conduct patient led research on long COVID
- 96% had PASC reported sx beyond 90 days
- Fatigue, cough, SOB, H/a, muscle aches, chest tightness, sore throat
- Most frequent sx after 6 months => fatigue, PEM, cog dysfunction
- Over 85% had relapses of sx with exercise, physical or mental activity, stress
- 42% reduced work schedule
- 22% had not returned to work

Davis, HE et al, Characterizing long COVID in an interactive cohort:7 months of symptoms and their impact. Eclinmedicine (38).101019

Expected recovery time:

- Depends upon severity of the acute illness
- Premorbid risk factors/health status
- Older patients, hospitalized patients, medical complications, prolonged stay in IU
- Fevers, chills, problems with taste and smell typically resolve in 2-4 weeks
- Fatigue, SOB, cognitive deficits and psychological effects may last for months
- Even relatively healthy young individuals may face long-term impacts from their illness

Things to keep in mind

- Talk to your provider – in general, should get vaccine
- Not infectious when having long covid
- Recognize need to support equitable access to care for all patients with post covid conditions -
- Recognize need to strengthen safety-net care that includes evaluation in some cases for disability/benefits
- Data suggests refutes the idea that young, healthy people will be fine after a covid 19 infection

References

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