Neurological Manifestations and Sequelae of COVID-19: Long-Term Implications

Mid-Atlantic Regional Conference in Occupational And Environmental Medicine
October 16, 2021

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Financial and Other Disclosures

- Grant Support: VA HSR&D Investigator Initiated Research Award-Addressing Sleep Apnea Post-Stroke (ASAP; IIR 16-211), VA Headache Centers of Excellence Research and Evaluation Center (HCoE REC) Partnered Award, VA Implementation Research Pilot - TelemEdiciNe-bAsed CognItive TherapY (TENACITY; IRP 20-002).

- The views expressed in this Grand Rounds are those of the presenter and do not necessarily represent the view of the Department of Veterans Affairs.
Financial and Other Disclosures

- Chicken owner
Outline for our Discussion

• Acute Neurological manifestations of SARS-CoV-2 infection

• Long COVID and sequelae of nervous system involvement in COVID-19
  – Cognition
  – Headache
  – Ischemic stroke

• Outpatient Management of Long COVID
  – Enhancing the ability for safe, full return to work
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Confirmed cases of COVID-19 worldwide and in USA as of Oct 4, 2021

Total Cases: 235,298,756
Total Deaths: 4,806,911

USA: 43,812,011 | 702,681

Johns Hopkins University Coronavirus Resource Center, Oct 4, 2021
Confirmed cases of COVID-19 Worldwide and in USA as of Oct 4, 2021

Click any country below to hide/show from the graph:
- United States
- United Kingdom
- Turkey
- Russia
- India
- Brazil
- Philippines
- Iran
- Malaysia
- Thailand

Johns Hopkins University Coronavirus Resource Center, Oct 4, 2021
• The spikes (red) on the surface of coronaviruses particle (blue) give this virus family its name – corona, which is Latin for “crown.”

• Spike proteins enable the virus to enter and infect human cells by binding to Angiotensin-converting enzyme 2 (ACE-2) receptors on human cells, the mammalian cell surface receptor that SARS-CoV-2 binds.

• Localization of ACE-2 receptors on human cells largely determines cellular tropism of virus (which cell types allow viral entry/infection).
Location of ACE2 Receptors in Humans

1. Non-keratinizing squamous epithelium of the nasopharynx
2. Type I and II alveolar epithelial cells of the lung
3. Proximal tubular cells of the kidney
4. Enterocytes of the small intestine
5. Endothelial cells lining arteries and veins throughout the body
6. Neurons and glial cells in the brain

Zubair et al, *JAMA Neurology*, 2020 Aug 1;77(8):1018-1027
Image by Lindsay McAlpine
**Hematogenous Spread.** SARS-CoV-2 may infect vascular endothelial cells which line the blood brain barrier, and spread to the surrounding astrocytes and neurons (A), or infiltrate the CNS via trafficking by infected leukocytes (B).

**Transcribial Route.** SARS-CoV-2 can infect the squamous epithelium of the nasopharynx and olfactory epithelium (A). SARS-CoV-1 may spread retrograde via a trans-synaptic transfer along olfactory nerve back across the cribriform plate into the olfactory bulb and brain (B).

*Zubair et al, JAMA Neurology, 2020 Aug 1;77(8):1018-1027*

*Image by Lindsay McAlpine*
Neurologic complications in acute COVID-19

- Yale Neuro COVID inpatient consult service → wide spectrum of neurological & psychiatric manifestations in patients with acute COVID-19

• Immune mediated neurological/psychiatric conditions in acute COVID-19
• Cerebrovascular injury in acute COVID-19

N=100

Zubair et al, *JAMA Neurology*, May 2020
Farhadian et al, *BMC Neurology*, June 2020
Sheth et al, *JAMA Neurology*, Sept 2020
McAlpine et al, *Stroke*, June 2021
Neurologic complications in acute COVID-19 - Demographics

125 hospitalized in UK-wide surveillance ‘CoroNerve’ study
- 62% cerebrovascular event
- 31% altered mental status
- 5% peripheral nerve or muscle disorder
- 2% other

Varatharaj et al, Lancet Psychiatry, Oct 2020
Stroke in young patients with COVID-19

5 patients <50 years of age with large vessel ischemic stroke as presenting symptom of COVID-19 to Mt. Sinai Hospital, New York, USA.

<table>
<thead>
<tr>
<th>Table 1. Clinical Characteristics of Five Young Patients Presenting with Large-Vessel Stroke.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
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<tr>
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</tr>
<tr>
<td>Age — yr</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Medical history and risk factors for stroke†</td>
</tr>
<tr>
<td>Fibrinogen — mg/dl</td>
</tr>
<tr>
<td>D-dimer — ng/ml</td>
</tr>
<tr>
<td>Ferritin — ng/ml</td>
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</tbody>
</table>

Reference ranges are as follows: platelet count, 150,000 to 450,000 per cubic millimeter; prothrombin time, 12.3 to 14.9 seconds; activated partial-thromboplastin time, 25.4 to 34.9 seconds; fibrinogen, 175 to 450 mg per deciliter; D-dimer, 0 to 500 ng per milliliter; and ferritin, 30 to 400 ng per milliliter. CT denotes computed tomography, CTA CT angiography, CTP CT perfusion imaging.

**COVID-19 →**
Coagulopathy (prolonged PT)
Thrombocytopenia
Pro-thrombotic state (elevation of D-Dimers)
ACE2 receptors on endothelial cells & pericytes lining the vessels → endothelial activation/vascular inflammation?
267 patients hospitalized in UK-wide surveillance study

- In 29%, neuro/psych symptoms predated the onset of COVID-19 symptoms
- In 47%, neuro/psych symptoms occurred after respiratory condition improved
Neurologic complications in acute COVID-19 – Timing of onset

267 patients hospitalized in UK-wide surveillance study
• Cerebrovascular
  ▪ n = 131 (49%)
• Central inflammatory
  ▪ n = 25 (9%)
• Psychiatric
  ▪ n = 25 (9%)

Russell Ross et al, Brain Communications, Oct 2020
Neurologic complications in acute COVID-19 – Timing of onset

267 patients hospitalized in UK-wide surveillance study
- Cerebrovascular
  - \( n = 131 \) (49%)

Cerebrovascular cases associated with COVID-19:
- Younger (<60 years of age)
- Greater number of modifiable cerebrovascular risk factors

Russell Ross et al, *Brain Communications*, Oct 2020
Neurologic complications in acute COVID-19 – Timing of onset

267 patients hospitalized in UK-wide surveillance study

- Cerebrovascular
  - n = 131 (49%)

Cerebrovascular cases associated with COVID-19 among younger patients:
- Presented with delayed onset from respiratory symptoms
- Higher rates of multi-vessel occlusion
- Higher rates of systemic thrombotic events

Russell Ross et al, *Brain Communications*, Oct 2020
Neurologic complications in acute COVID-19 – Timing of onset

267 patients hospitalized in UK-wide surveillance study

- Other central disorders (N=95; 36%)
  - Delirium n = 28 (11%)
  - Central inflammatory n = 25 (9%)
  - Psychiatric n = 25 (9%)
  - Other encephalopathies n=17 (7%)
    - Severe encephalopathy not meeting criteria for delirium n = 28 (28%)
Neurologic complications in acute COVID-19 – Timing of onset

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Severe encephalopathy (versus those with delirium):
  - Younger
  - Higher rates of admission to ICU
  - Longer duration of ventilation

Russell Ross et al, Brain Communications, Oct 2020
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Overview

Although most people with COVID-19 get better within weeks of illness, some people experience post-COVID conditions. **Post-COVID conditions** are a wide range of new, returning, or ongoing health problems people can experience **four or more weeks** after first being infected with the virus that causes COVID-19. Even people who did not have COVID-19 symptoms in the days or weeks after they were infected can have post-COVID conditions. These conditions can present as different types and combinations of health problems for different lengths of time.

These post-COVID conditions may also be known as long COVID, long-haul COVID, post-acute COVID-19, long-term effects of COVID, or chronic COVID. CDC and experts around the world are working to learn more about short- and long-term health effects associated with COVID-19, who gets them, and why.

As of July 2021, “long COVID,” also known as post-COVID conditions, can be considered a disability under the Americans with Disabilities Act (ADA). Learn more: [Guidance on “Long COVID” as a Disability Under the ADA, Section I](https://www.hhs.gov).
CDC Definition of Post-COVID Conditions

- Difficulty breathing or shortness of breath
- Tiredness or fatigue
- Symptoms that get worse after physical or mental activities (also known as post-exertional malaise)
- Difficulty thinking or concentrating (sometimes referred to as “brain fog”)
- Cough
- Chest or stomach pain
- Headache
- Fast-beating or pounding heart (also known as heart palpitations)
- Joint or muscle pain
- Pins-and-needles feeling
- Diarrhea
- Sleep problems
- Fever
- Dizziness on standing (lightheadedness)
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- Mood changes
- Change in smell or taste
- Changes in menstrual period cycles

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Neuropsychiatric issues after recovery from acute COVID-19

The New York Times

‘I Feel Like I Have Dementia’: Brain Fog Plagues Covid Survivors
The condition is affecting thousands of patients, impeding their ability to work and function in daily life.
By Pam Belluck

Science
From ‘brain fog’ to heart damage, COVID-19’s lingering problems alarm scientists
By Jennifer Couzin-Frankel | Jul. 31, 2020, 1:30 PM

Neurologic and Psychiatric Effects of SARS-CoV-2 Meeting
July 14-15, 2021
Neuropsychiatric issues after recovery from acute COVID-19

Characterizing long COVID in an international cohort: 7 months of symptoms and their impact

3,762 respondents with confirmed or suspected COVID-19 from 56 countries completed survey via online support groups and social media.

Davis et al, *EClinicalMedicine*, June 2021
Neuropsychiatric issues after recovery from acute COVID-19

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3,762 respondents with confirmed or suspected COVID-19 from 56 countries completed survey via online support groups and social media.
Neuropsychiatric issues after recovery from acute COVID-19

3,762 respondents with confirmed or suspected COVID-19 from 56 countries completed survey via online support groups and social media.

- 91% of respondents reported time to recover in excess of 35 weeks.
- Most frequent symptoms after month 6 included:
  - Fatigue
  - Post-exertional malaise
  - Cognitive dysfunction

Davis et al, *EclinicalMedicine*, June 2021
Neuropsychiatric issues after recovery from acute COVID-19

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3,762 respondents with confirmed or suspected COVID-19 from 56 countries completed survey via online support groups and social media.

- 45.2% required reduced work schedule compared to pre-illness
- 22.3% were not working at the time of survey due to illness
- 88% continued to report cognitive dysfunction or memory issues (across all ages groups)

Davis et al, EClinicalMedicine, June 2021
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Davis et al, *EClinicalMedicine*, June 2021
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PATIENT LED RESEARCH
For COVID-19

e. Short-term memory loss
Long-term memory loss
Other Memory Symptoms
Forgetting how to do routine tasks
Inability to make new memories

f. Memory

Davis et al, EClinicalMedicine, June 2021
Neuropsychiatric issues after recovery from acute COVID-19

Characterizing long COVID in an international cohort: 7 months of symptoms and their impact

PATIENT LED RESEARCH
For COVID-19

Davis et al, EClinicalMedicine, June 2021
Regional cerebral functional & structural changes in post-COVID-19 neurologic syndromes

**Regional cerebral hypometabolism**

- 45 participants with persistent symptoms median 3 months (range 26-155 days) after onset acute COVID-19 → regional hypometabolism on $^{18}$F- FDG PET compared to 44 healthy controls.

- PET metabolic values associated with symptoms (memory, pain, anosmia, etc.).

Regional cerebral functional & structural changes in post-COVID-19 neurologic syndromes

Regional gray matter atrophy
782 participants from the UK Biobank COVID-19 re-imaging study
- 394 participants tested positive for SARS-CoV-2 between their two scans
- 388 controls matched for age, sex, ethnicity and interval between scans

Loss of gray matter -
parahippocampal gyrus, orbitofrontal cortex and insula, anterior cingulate cortex, supramarginal gyrus and temporal pole.

Douaud et al, MedArchive preprint, 2021
Headache and COVID-19
Headache Prevalence and Disability

Prevalence and burden of self-reported migraine and severe headache are high within the adult US population

- 1 out of 6 Americans and 1 out of 5 women
- Prevalence has been stable for nearly 2 decades

Headache is consistently the fourth or fifth most common reason for visits to the emergency room

Migraine is the second highest cause of disability associated life years (DALYs) and the leading cause of DALYs for young women

Burch et al., *Headache*, April 2018
Steiner et al., *Journal of Headache Pain*, December 2020
Characterizing long COVID in an international cohort: 7 months of symptoms and their impact

**PATIENT LED RESEARCH**
For COVID-19

- Headaches, behind the eyes
- Headaches, diffuse
- Headaches, in the temples
- Headaches, at the base of the skull
- Headaches/pain after mental exertion
- Migraines
- Headaches/other

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Davis et al, *EclinicalMedicine*, June 2021
4.10 New daily persistent headache (NDPH)

Previously used terms:

Chronic headache with acute onset; de novo chronic headache.

Description:

Persistent headache, daily from its onset, which is clearly remembered. The pain lacks characteristic features, and may be migraine-like or tension-type-like, or have elements of both.

Diagnostic criteria:

A. Persistent headache fulfilling criteria B and C
B. Distinct and clearly-remembered onset, with pain becoming continuous and unremitting within 24 hours
C. Present for >3 months
D. Not better accounted for by another ICHD-3 diagnosis\(^1;2;3;4\).
COVID-19 may worsen preexisting primary headache conditions
  • Nearly 75% reported having a primary headache condition prior to COVID-19 (89/121)
    • 65% experienced migraine headaches
    • 11% experienced tension type headache

Preexisting headache conditions worsened after COVID-19
  • 55% reported worsening of their prior headache condition
    • Increase in migraine attack severity
    • Increase in migraine attack frequency
    • Increase in average days of analgesic use

De novo Headache after COVID-19 (n=32)
  • 55% reported worsening of their prior headache condition
    • Migraine 62.5% (n=20)
    • Tension-type headache 37.5% (n=12)
Global studies of post-COVID-19 neurologic syndromes
- UK COVID CNS Study - 1300 participants (800 COVID/500 controls) for clinical and blood sampling
- US military telephone survey collecting neuropsych/mental health data from thousands of deployed individuals worldwide
- NINDS intramural neurologic signs/symptoms survey
- Alzheimer's Association - international consortium to study consequences of SARS-CoV-2 on the CNS with relevance to AD and other dementias
- NIH/NINDS-funded COVID-19 Neuro Databank/Biobank (NYU Langone)
- NIH Post-Acute Sequelae of SARS-CoV-2 (PASC) initiative – RECOVER Study
Functional Recovery After Ischemic Stroke

General trajectories of Stroke Recovery
- 10% of survivors recover soon after their event
- 25% recover with some minor physical impairments
- 40% have moderate to severe impairments
- 10% need care in a long-term care facility
- 15% do not survive

https://www.strokeaids.com/recovery-rehabilitation-and-resources-after-a-stroke/
Ischemic stroke is a major cause of functional impairment

- Most functional gains occur within the first 12 weeks
- Functional recovery ‘plateaus’ 5-6 months post-cerebrovascular event
- Cognitive function tends to improve earlier than motor function
  - 65% experienced migraine headaches
  - 11% experienced tension type headache
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“Long COVID” as a Disability

Guidance on “Long COVID” as a Disability Under the ADA, Section 504, and Section 1557

Although many people with COVID-19 get better within weeks, some people continue to experience symptoms that can last months after first being infected, or may have new or recurring symptoms at a later time. \(^1\) This can happen to anyone who has had COVID-19, even if the initial illness was mild. People with this condition are sometimes called “long-haulers.” This condition is known as “long COVID.” \(^2\)

In light of the rise of long COVID as a persistent and significant health issue, the Office for Civil Rights of the Department of Health and Human Services and the Civil Rights Division of the Department of Justice have joined together to provide this guidance.

This guidance explains that long COVID can be a disability under Titles II (state and local government) and III (public accommodations) of the Americans with Disabilities Act (ADA), \(^3\) Section 504 of the Rehabilitation Act of 1973 (Section 504), \(^5\) and Section 1557 of the Patient Protection and Affordable Care Act (Section 1557). \(^6\) Each of these federal laws protects people with disabilities from discrimination. \(^6\) This guidance also provides resources for additional information and best practices. This document focuses solely on long COVID, and does not address when COVID-19 may meet the legal definition of disability.

The civil rights protections and responsibilities of these federal laws apply even during emergencies. \(^7\) They cannot be waived.

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Step 1: Stay in Touch while the Worker is Absent from Work

Supporting Return to Work

Step 2: Prepare for the Worker’s Return

- Consider the cognitive load of work duties and his/her capacity to resume prior duties.
- Consider possible headache triggers (e.g., bright lights, increased screen time).

Step 2: Prepare for the Worker’s Return

- Are there neurological deficits that would make it difficult to resume prior duties and/or drive (e.g., hemiparesis, vision loss, aphasia, post-stroke depression and urinary incontinence).

Step 3: Have a Return-to-Work Conversation

- List work demands and consider listing them under categories of cognitive, physical, and emotional.
- Seek to understand their concerns and needs.

Step 4: Provide Support During the Early Days of the Return to Work

- Permission to take things slowly.
- Regular check-ins about how they are managing their health and work.

Supporting Return to Work

Step 5: Provide Ongoing Support and Review Regularly
- Review workloads.
- Communicate regularly and openly.

Supporting Return to Work

Exemplar Job Modifications:

• Phased return and working hours.
• May continue to be actively engaged in rehabilitation.
• Altering work patterns, timing, and hours.

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