
Headaches in Post-Acute Sequelae of COVID-19



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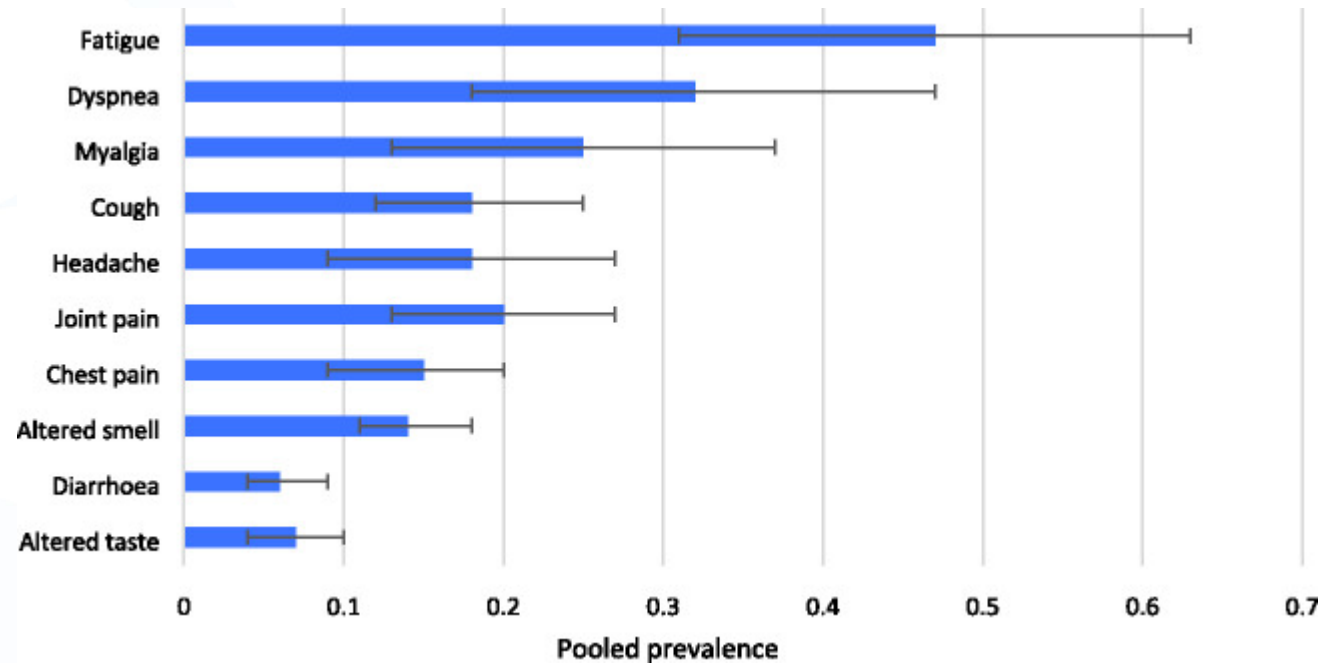
University of Utah Health Project ECHO

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Headache Prevalence

Systematic review of articles describing persistent COVID-19 symptoms in 2021 suggested that headache was the **fifth most common symptom** of long-COVID with a prevalence of **18%**

Pooled prevalence for the 10 most common symptoms in patients with long-COVID



Headache Prevalence

- Overall frequency of long-COVID headache seems to be similar in patients who were hospitalized vs managed in the outpatient setting for their acute infection
- Treatment-resistant headaches during acute infection, however, are associated with development of post-COVID headaches



Patients who had persistent headaches at 9 months compared to those with headaches during acute infection:

- More frequently female (75.7%)
- Generally in “middle age” (52 years old)
- Lower frequency of COVID pneumonia during acute infection (36.4% vs 47.9%)

Headache Prevalence

- A cross-sectional study found persistent headache in 50% of patients experiencing hyposomnia and sleep impairment months after recovery of acute COVID-19 infection
- Begs the question of whether there might be a common pathophysiological substrate



Impairments in Those With Headaches

People suffering from long-COVID headaches showed a higher percentage of disability and greater limitations in activities such as:

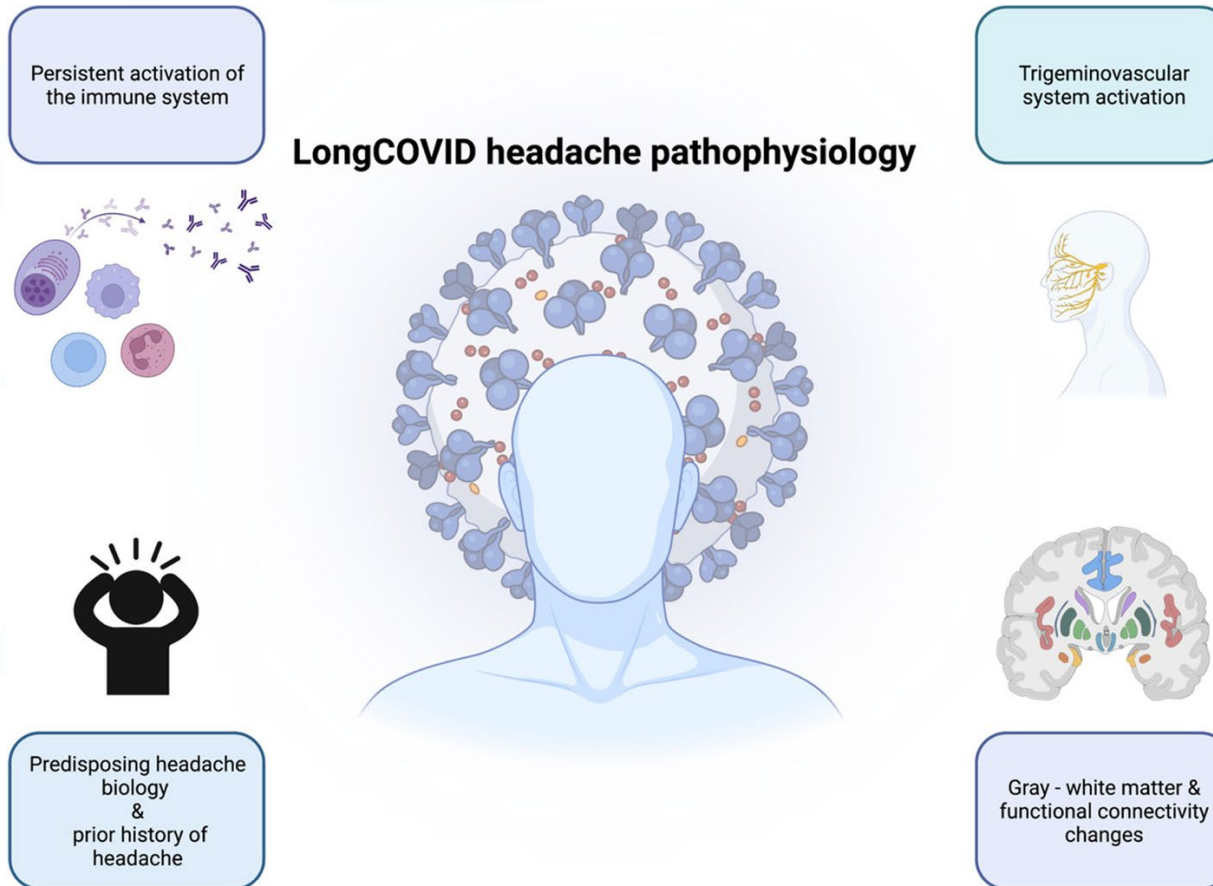
- Meal preparation
- Cleaning
- Laundry
- Household repairs



Additional prevalent limitations include:

- Ability to express oneself
- Ability to understand conversations
- Impaired reading and writing

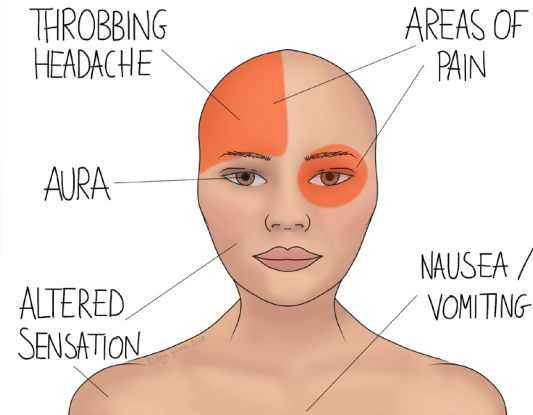
Proposed Pathophysiological Mechanisms for Long-COVID Headache



Hypothesis: Trigeminovascular System Activation

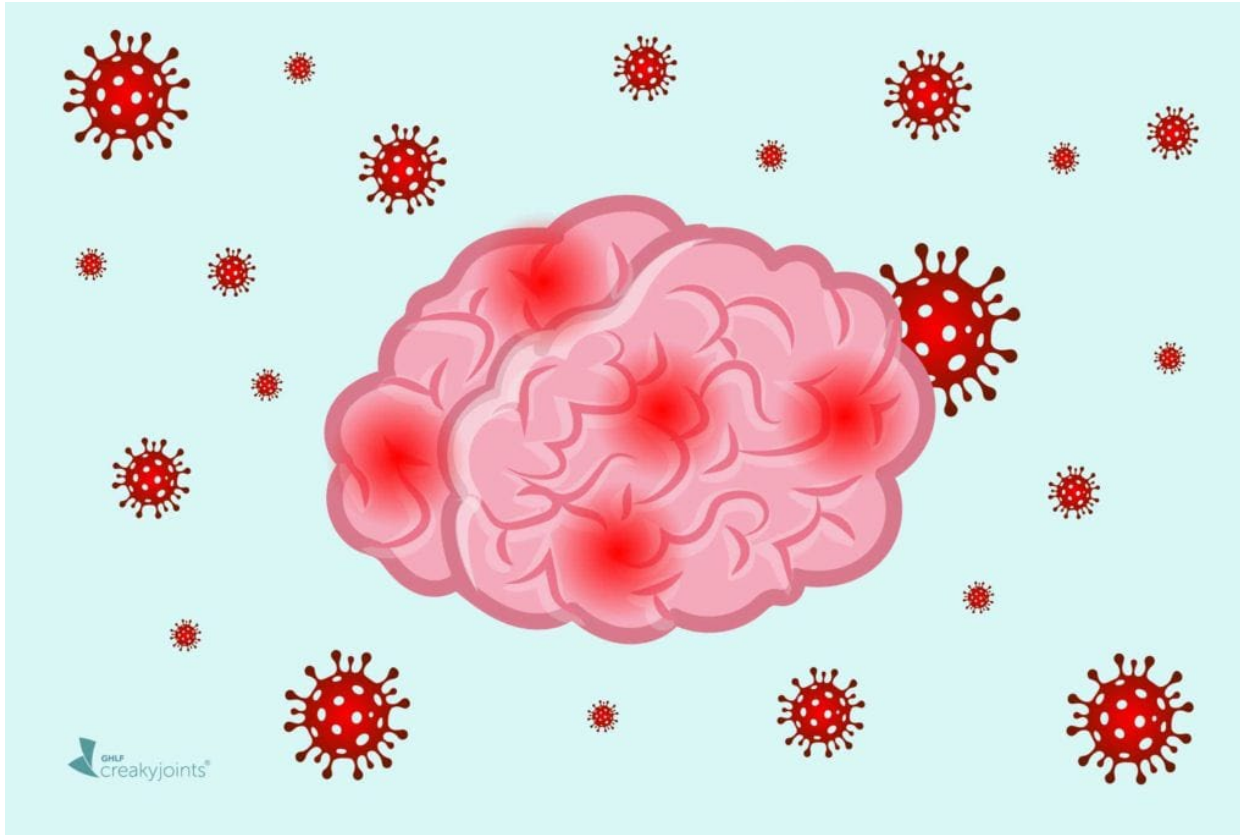
Phenotypic Headache Qualities in Long-COVID persistent headache at 9 months (compared to headache during acute infection):

- Throbbing quality
- Lower frequency of “pressing” quality
- Higher frequency of phonophobia/photophobia
- Higher frequency of worsening of symptoms with physical activity
- These qualities are thought to be consistent with our current understanding of migrainous headaches



- One case-control study observed that patients with a prior history of migraine had 40% more frequent “long-lasting headaches” as defined by continuous headache for >1 day duration
- “Activation” of a pre-existing risk for or genetic predisposition to migraine through the trigeminovascular system has thus been proposed as a causative or contributory mechanism

Hypothesis: Immune System Activation



- Presence of headache during acute phase of COVID-19 infection has been associated with lower mortality, lower ICU admission rates, and a better overall prognosis
- These patients had lower blood levels of D-dimer, C-reactive protein, lactate dehydrogenase, and ferritin (all acute phase reactants)
- These patients also had higher blood lymphocyte levels
- Findings thought to be emblematic of a more efficient and robust immune response to initial infection

Hypothesis: Immune System Activation

- Hypothesized that patients with long-COVID may manifest persistent immune activation and biohumoral response to continued presence of viral antigens or RNA persisting in extrapulmonary tissues despite the absence of fully-operational viruses
- Autopsy study of 44 patients used highly sensitive viral nucleic acid assays to discover viral RNA in tissues throughout the body (**including the brain**) up to 230 days after acute COVID-19 in **all** patients even when the virus itself was undetectable in blood or in patients with only mild COVID-19 infection
- Persistence of detectable viral RNA is much greater in those with long-COVID compared to recovered COVID



Hypothesis: Structural & Functional Brain Changes

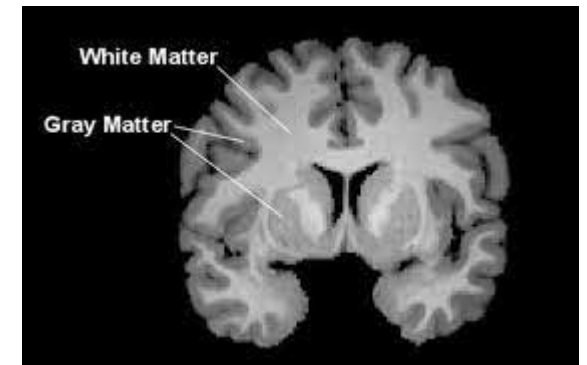
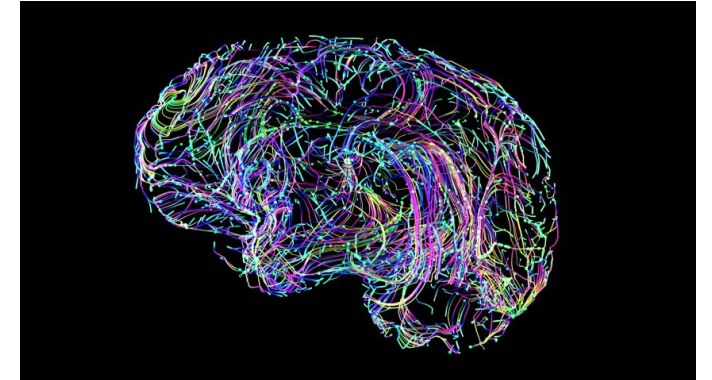
Longitudinal project studying brain structure and cognitive function of 785 participants over time using neurophysiological and MRI information allowed for pre- and post-COVID pandemic evaluation of both participants who were and were not infected with SARS-Cov-2

- Gray matter reduction, specifically in the orbitofrontal cortex and parahippocampal gyrus of those s/p COVID infection
- High cortical surface area and gray matter volume in the orbitofrontal cortex in those with long-COVID headache specifically, suggesting some gray matter changes could be correlated with specific long-COVID manifestations



Hypothesis: Structural & Functional Brain Changes

- Resting-state functional connectivity has observed weakened functional connections between the cingulate, hippocampal, parietal, temporal, and frontal gyri and strengthened functional connectivity with the occipital regions
- White matter changes with higher axial diffusivity in the corona radiata and internal and external capsules
- Areas of the brain detected to be hypometabolic including the right parahippocampal gyrus, the **brainstem**, the thalamus, the amygdala, the orbital gyrus, the olfactory gyrus, and the temporal lobe → though no specific metabolic studies in long-COVID headache specifically



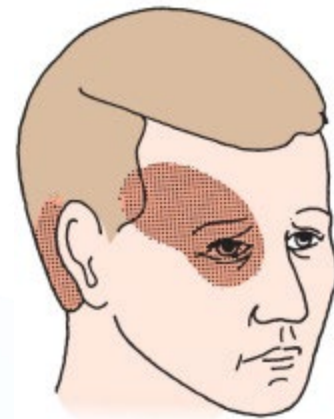
Planchuelo-Gómez A, García-Azorín D, Guerrero Peral AL, Aja-Fernández S, Rodríguez M, Moro R, de Luis-García R (2021) Gray matter cortical changes in patients with persistent headache after COVID-19 infection: an exploratory study. The International Headache Congress - IHS and EHF joint congress 2021 : Virtual. 8–12 September 2021. J Headache Pain 22(Suppl 1):103

Sollini M, Morbelli S, Ciccarelli M, Cecconi M, Aghemo A, Morelli P, Chiola S, Gelardi F, Chiti A (2021) Long COVID hallmarks on [18F]FDG-PET/CT: a case-control study. Eur J Nucl Med Mol Imaging 48(10):3187–3197

Tana, Claudio, et al. "Long Covid Headache." *The Journal of Headache and Pain*, vol. 23, no. 1, 2022, <https://doi.org/10.1186/s10194-022-01450-8>.

Clinical Features

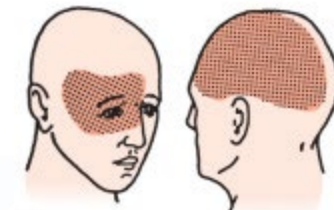
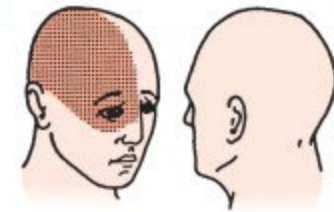
- No one specific clinical phenotype
- Topography of oppressive symptoms predominantly bilateral with frontal or periorcular predominance (though only limited cross-sectional study data available)
- Throbbing quality seen in 1/3 of patients
- Temporal and occipital predominant topography are also described...



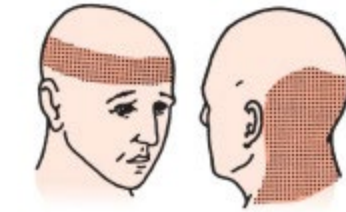
Common locations of migraine headache—tension headache may also be unilateral



Common locations of tension headache—migraine may occur in the same location



A



B "Hatband" distribution Occipital distribution

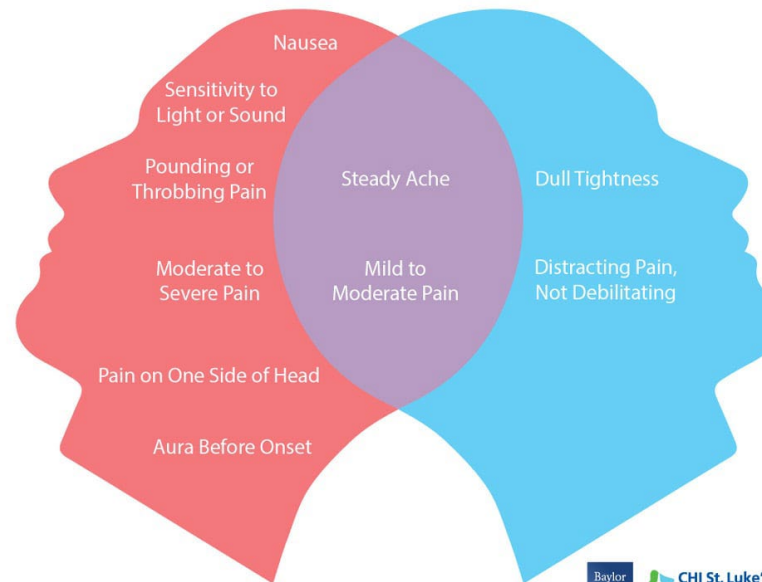
Clinical Features

- People *with* prior history of headaches usually report worsening of their underlying headaches
- People *without* headache history or acute infection headache can develop long-COVID headaches that often-fit current definitions for “new daily persistent headaches”

Many long-COVID headaches mimic primary headache phenotypes:

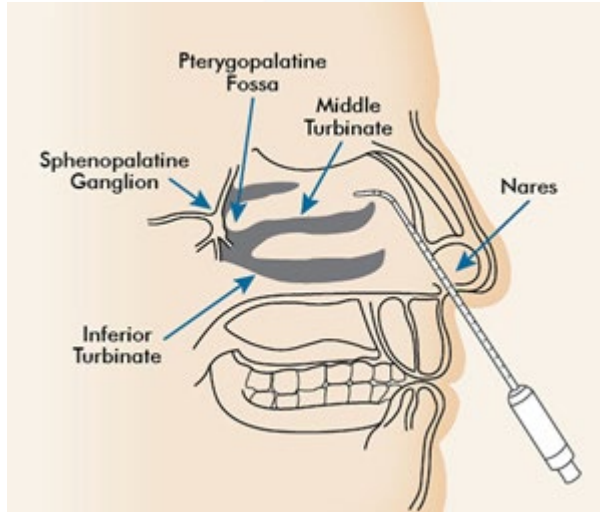
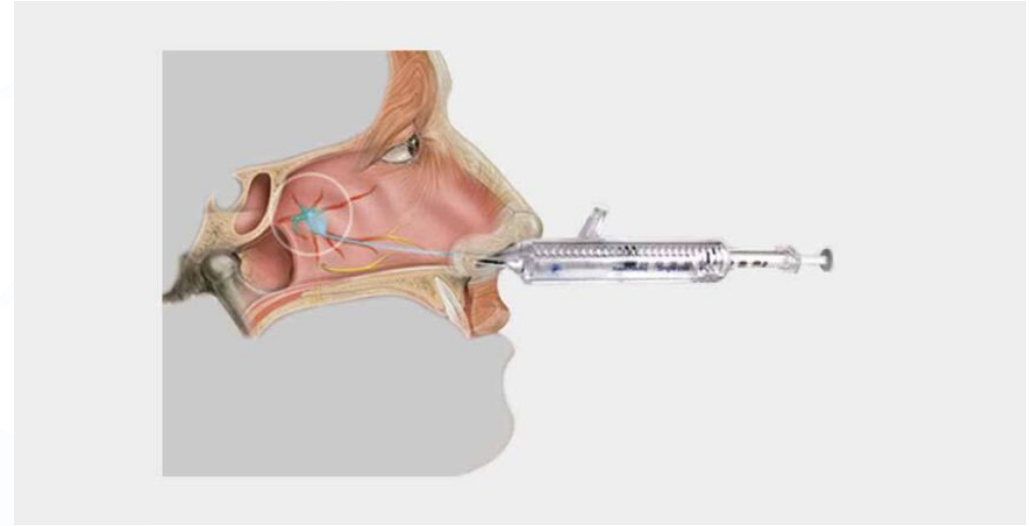
- Tension-type headaches
- Migraine-like headaches
 - Associated N&V, photophobia, phonophobia, worsening with physical activity
- No cluster headache phenotypes

Migraine vs Tension Headache



Treatment

Currently only **one** study listed on clinicaltrials.gov investigating the effect of sphenopalatine ganglion block with local anesthetics to reduce long-COVID headache



- Sphenopalatine ganglion is an extracranial parasympathetic ganglion located in the pterygopalatine fossa of the skull
- Has been evaluated for treatment of cluster headaches, trigeminal neuralgia, migraine headaches, usually within grade 2B evidence for its use
- Now, most commonly administered transnasally by a thin plastic tube delivering the anesthetic

Treatment

Most current treatment recommendations are extrapolated on the basis of evidence for available primary headaches with similar clinical phenotypes....

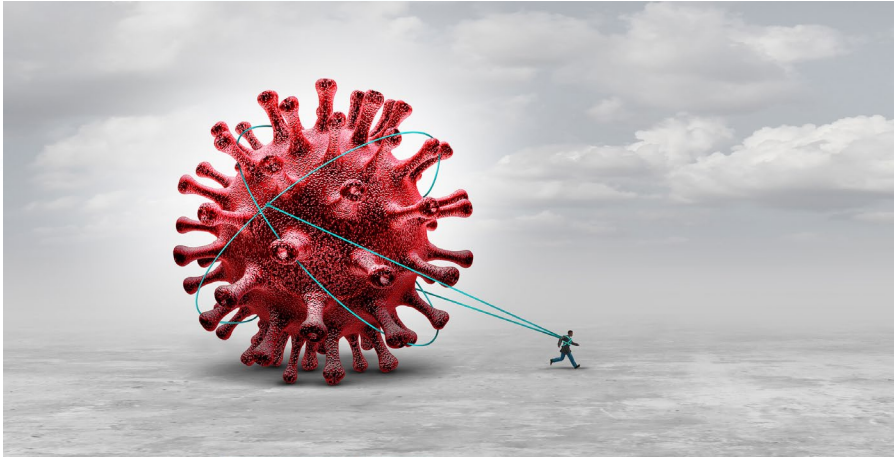


Out with the literature-based
evidence....

...In with the clinical experience of
a post-viral illness specialist

Practical Assessment & Management

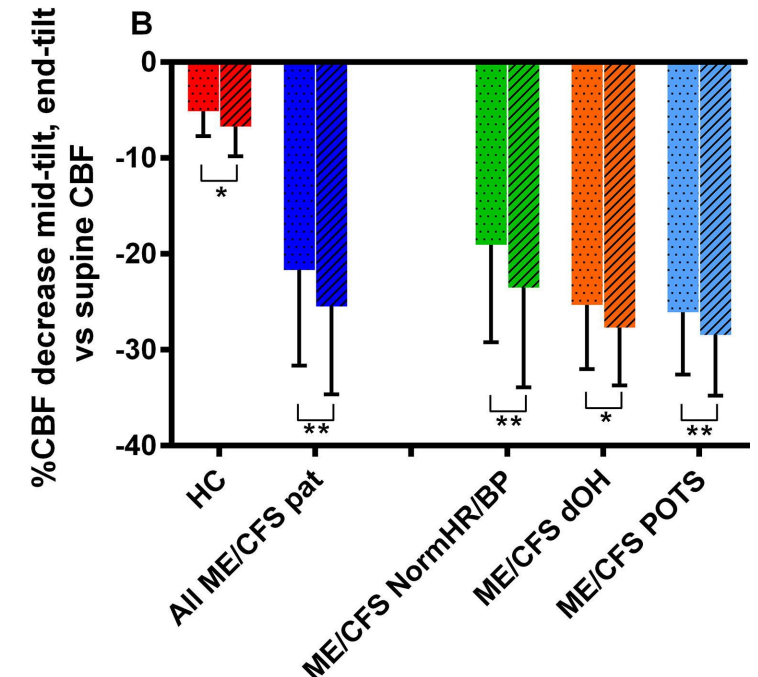
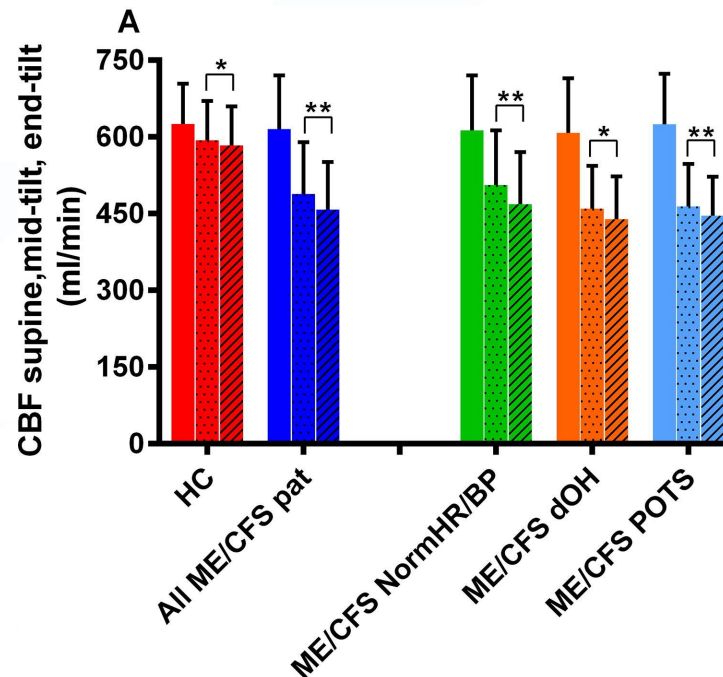
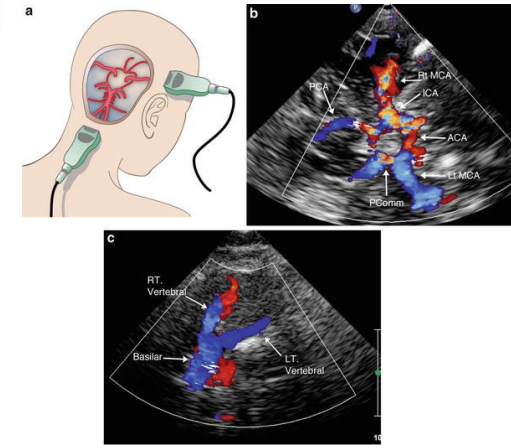
Start by considering the most common co-morbidities and risk factors in long-COVID....



Could any of these conditions/complications be contributing to headaches?

Orthostatic Headache?

- In an adolescent headache clinic, presence of orthostatic headache is 89.2% sensitive and 78.8% specific for a diagnosis of POTS
- Using doppler ultrasound to measure cerebral blood flow, Van Campen et. al showed a clinically significant reduction in blood flow during head-up tilt table testing in those with ME/CFS compared to healthy controls (26% vs 7%) even in the absence of significant HR and BP changes during tilt

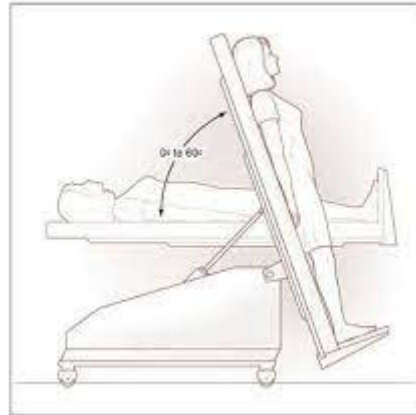


Orthostatic Headache?

Is the headache worse after being upright?



Does the headache develop as the day goes on?



Is the headache relieved with improved intravascular volume or other treatments directed at reduced cerebral blood flow?

- Trial of IV normal saline
- Oral fluid and sodium supplementation
- Compression clothing
- Fludrocortisone
- Pyridostigmine
- Midodrine/Droxidopa

Orthostatic Headache?

Alternatively, is the headache worse after laying down all night?

Is there a “pressure sensation” within the head expanding in all directions after treatment with measures for orthostatic intolerance?

Is there underlying hypertension and could the patient be experiencing supine hypertension?

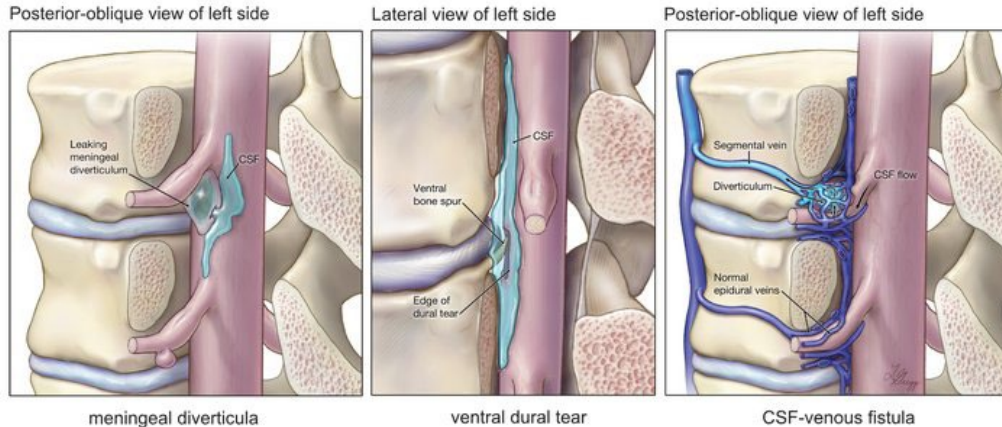


Consider medication-exacerbated supine hypertension (midodrine/droxidopa, vasoconstrictive decongestants, stimulant therapies, etc.)

Consider impairments to venous outflow. MR venogram?

Consider dysautonomia driven supine hypertension

Orthostatic Headache?



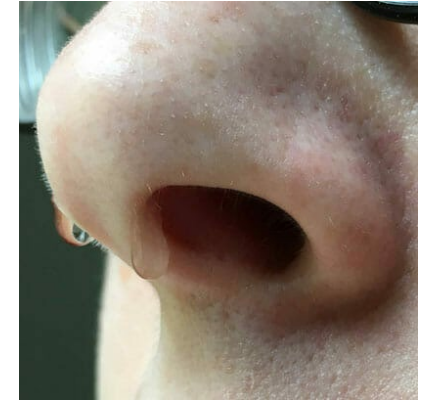
Types of spontaneous spinal CSF leaks

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Kranz PG et al. Neuroimaging Clin N Am. 2019 Nov;29(4):581-594.
doi.org/10.1016/j.nic.2019.07.006

Don't Forget CSF Leak:

- Most common symptom is rhinorrhea
- Symptoms increase with Valsalva and head-down maneuvers
- More common in those with idiopathic intracranial hypertension, Marfan's, EDS
- Brain MRI may show features of craniospinal hypotension
- Gold-standard imaging is CT Cisternography
- Treat with blood patch?



Mathias, Tiffany, et al. "Contemporary approach to the diagnosis and management of cerebrospinal fluid rhinorrhea." *Ochsner Journal* 16.2 (2016): 136-142.

Mokri, Bahram. "Spontaneous low pressure, low CSF volume headaches: spontaneous CSF leaks." *Headache: The Journal of Head and Face Pain* 53.7 (2013): 1034-1053.

Starling, Amaal, et al. "Sensitivity of MRI of the spine compared with CT myelography in orthostatic headache with CSF leak." *Neurology* 81.20 (2013): 1789-1792.

Tension Headache?

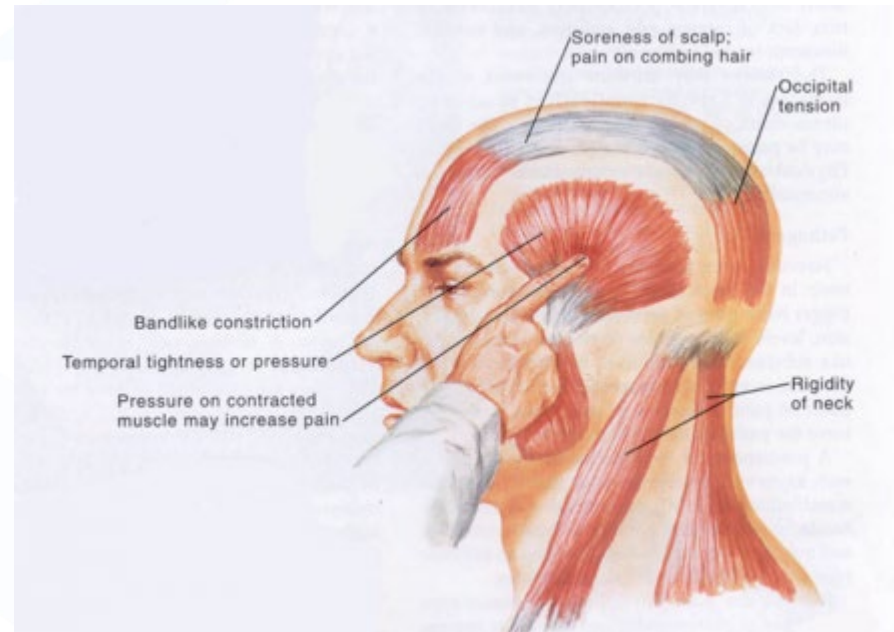
Does the patient have a connective tissue disorder (hEDS?) that predisposes to increased neck tension and bracing with movement and upright posture?

Is the patient experiencing sympathetic overdrive with increased muscle tension?

Do the patient's symptoms improve with heat, massage, stretching, muscle relaxants, acupuncture, botox?

Is there a “cape-like” distribution to pain with radiation along the trapezius, shoulders, intrascapular areas?

Is there pain with chewing, or at the TMJ, or with palpation of the temporalis, masseters, etc. (not consistent with true TMJ or with giant cell arteritis)?



Migraine Headache?

Does the patient experience aura?

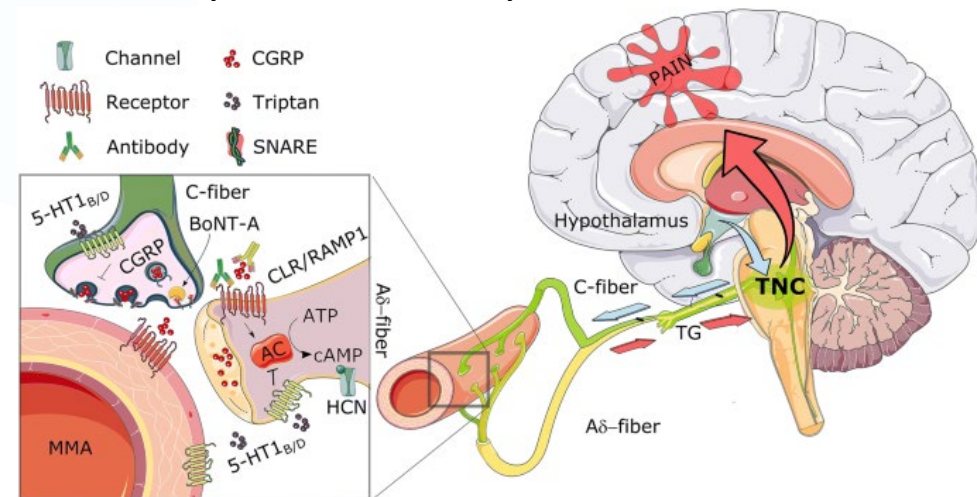
Is there phonophobia/photophobia?

Does the patient have mast cell activation syndrome (MCAS) or other mast cell dysfunction/hyperreactivity?

Catamenial component to headache?

Treatment:

- TCA's
- Beta blockers
- Topiramate
- CGRP antagonists
- Triptans
- Botox
- MCAS therapies → particularly compounded systemic cromolyn

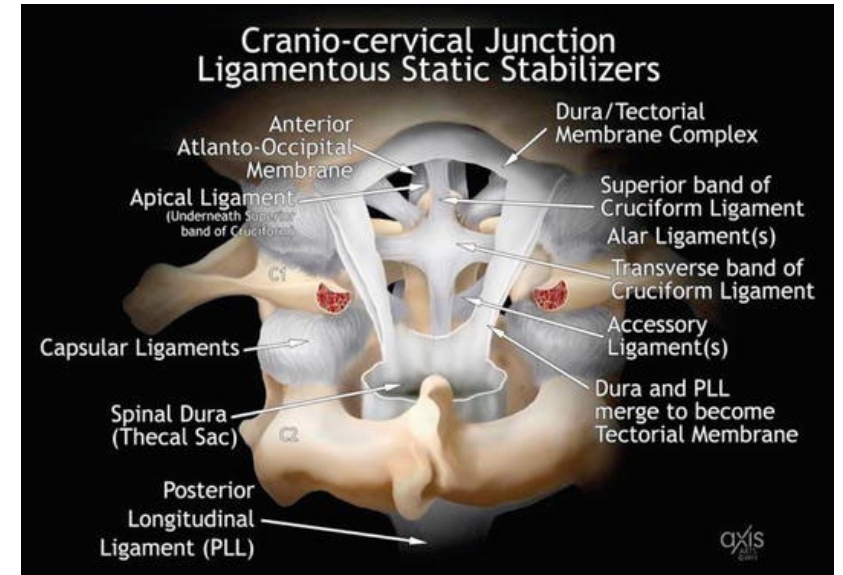
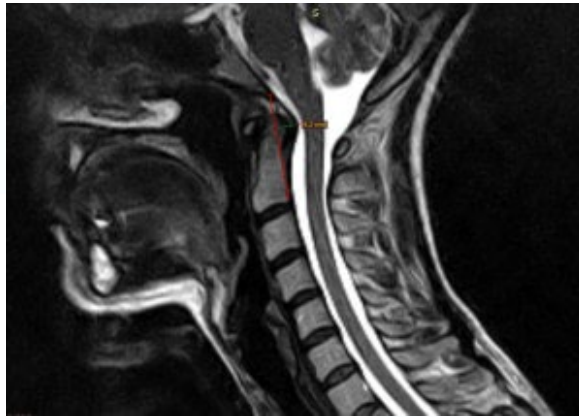


Remember: Migraines can be a **secondary complication** of other underlying headache or even non-headache pathophysiology and may ultimately be triggered by the presence or exacerbation of these other clinical manifestations

Craniocervical Instability/Atlanto-Axial Instability?

Acquired abnormalities of the occipital bone, foramen magnum, or first two cervical vertebrae and their supporting soft tissue structures that decreases the space for the cerebellum, the lower brain stem, or the cervical spinal cord with associated temporary or chronic pathological compression and/or deformation

May not be solely anatomical in pathophysiology, as this compression, stretch, or deformation of neurological structures may also cause a local or systemic immune response or local inflammatory response → consider local mast cell activation syndrome both worsening connective tissue and nervous tissue integrity and function



Craniocervical Instability/Atlanto-Axial Instability?

Does the patient experience a sensation that their head is too heavy to hold up or a “bobblehead” sensation?

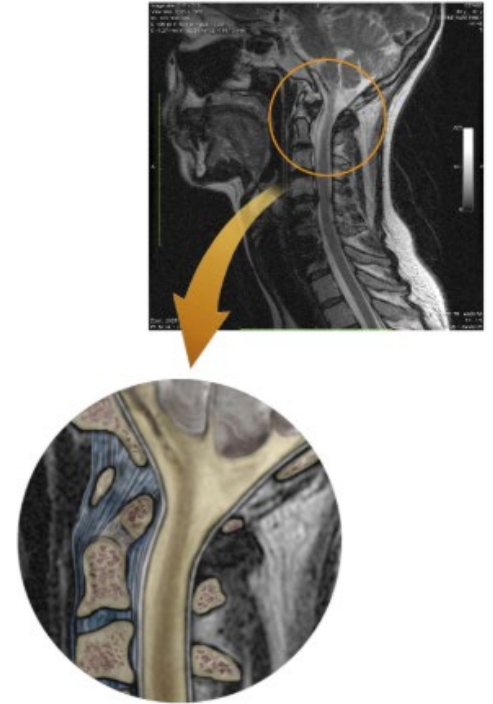
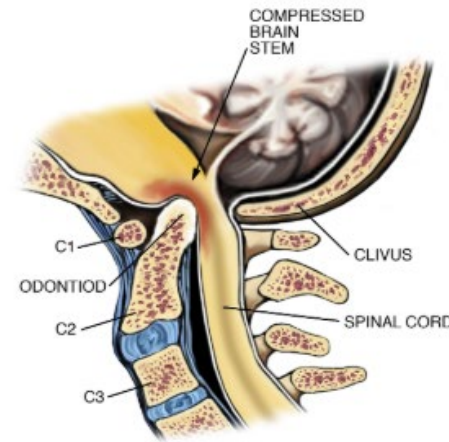
Are symptoms exacerbated with cervical rotation, flexion, extension, with bending over, with riding in a car (considering the bumps)?

Does the patient have extensive dysautonomia symptoms with little response to traditional pharmacotherapies?

Has the patient ever had a whiplash injury?

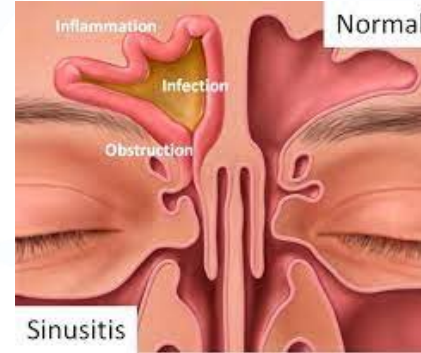
Has the patient ever noted relief of headaches or of other symptoms (brain fog, fatigue, etc.) of long-COVID with cervical traction-based manipulations?

Consider in those with connective tissue disorders and hypermobility, as it is estimated that 1 in 15 people with hEDS may go on to develop some degree of CCI/AAI



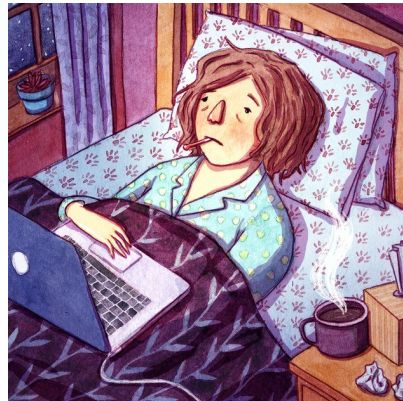
Other Pertinent Considerations...

Does the patient experience sinus congestion and pressure (perhaps in the setting of MCAS?)



Is there significant sleep disruption leading to headaches related to sleep deprivation?

Is the patient experiencing headache associated with other “viral reactivation-like” symptoms such as fever, arthralgia, myalgia, cervical LAD?



Other Pertinent Considerations...

Is the patient experiencing a mast cell-mediated response to something ingested (medication or food) or something smelled with signal transduction through the nervous system?



Is the patient experiencing hypoxia from sleep apnea, cardiopulmonary disease, etc.?



Could the patient be experiencing hypertensive urgency with headache and vision changes, possibly mediated by sympathetic overdrive?



Is the patient experiencing headaches secondary to excessive sensory processing sensitivity (bright lights, loud sounds, multiple sensory inputs at once)?

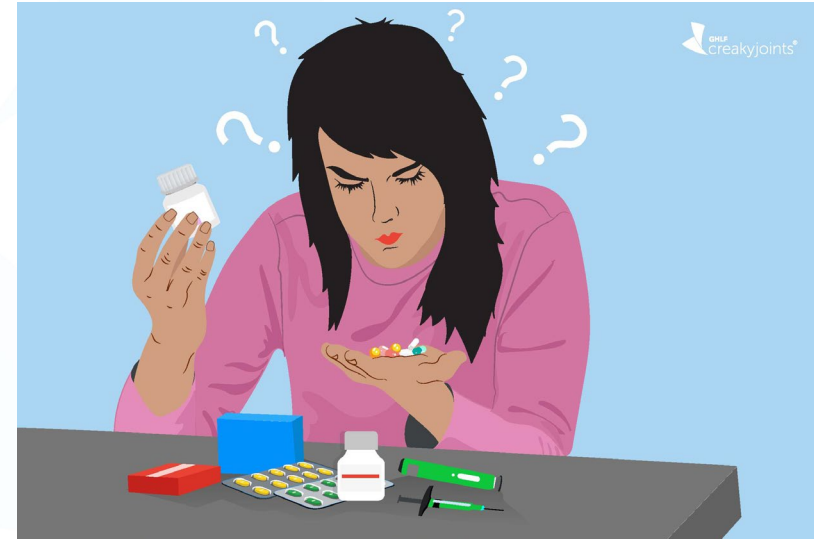


Other Pertinent Considerations...

Could the patient be experiencing medication overuse headache, particularly if taking OTC's or prescriptions for other sources of pain?

Could the patient be experiencing medication rebound headaches when medications are wearing off (particularly those used to manage OI and sympathetic overdrive) or in the setting of having forgotten to take medications?

Does the patient have structural TMJ abnormalities, perhaps mediated by underlying soft tissue laxity?

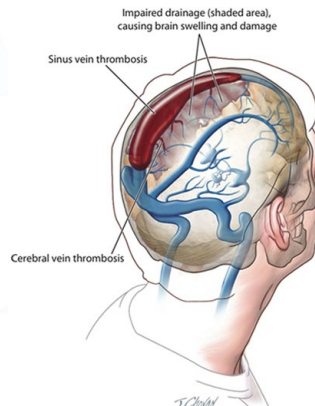


Don't forget.... Not all Headaches May Be Attributable to Long-COVID!

Glaucoma headache?



Stroke/Venous Sinus Thrombosis?



Trauma, perhaps from fall (syncopal, weakness...)?



Giant Cell Arteritis?



And Finally....

Lecture-Induced Headache

Thank You!

