POST-VIRAL ILLNESS AND COVID-19

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HOW COMMON ARE POST-COVID-19 "LONG HAULERS" ALSO CALLED "LONG COVID?"

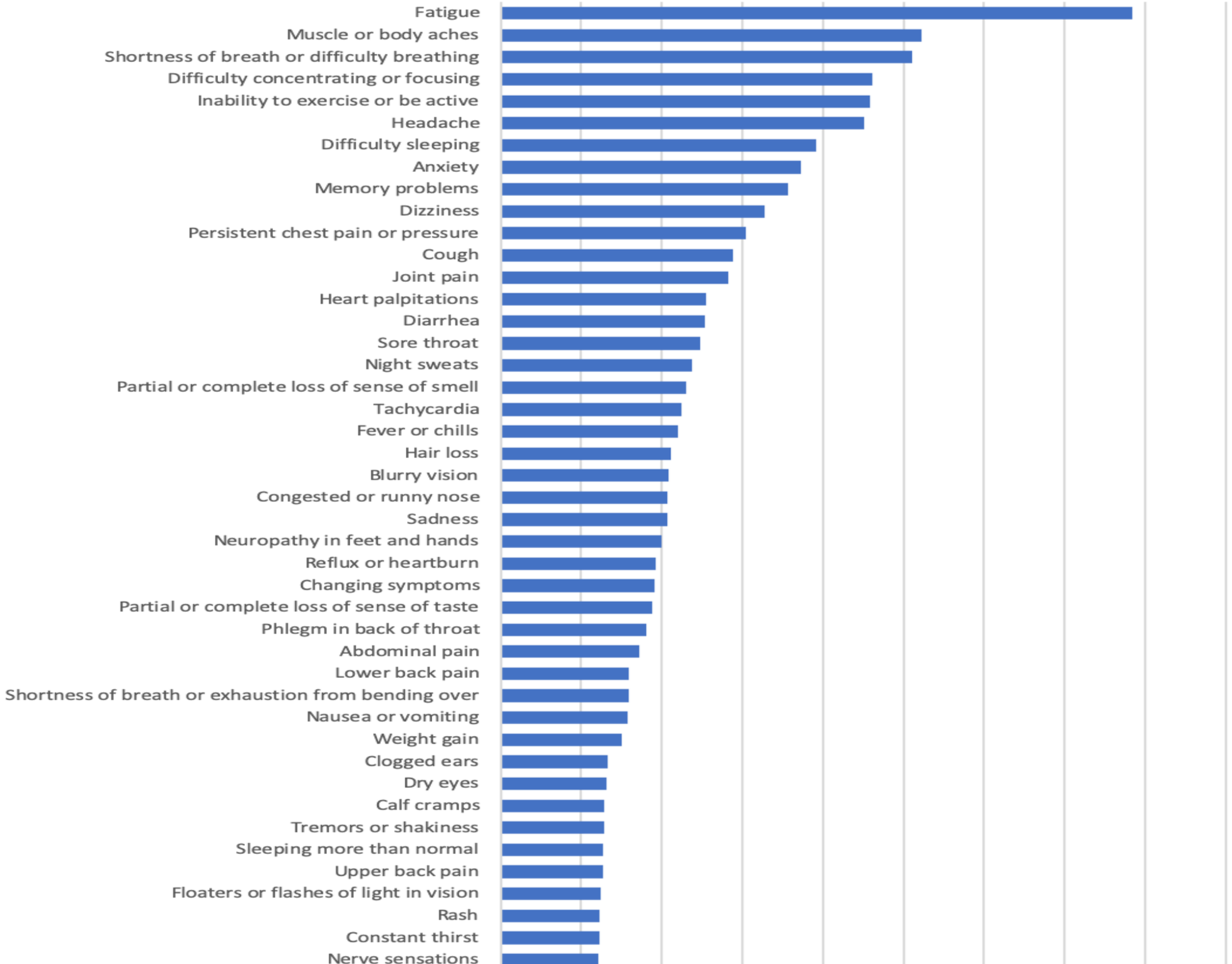
- An **online survey of about 1,500 people** with confirmed or suspected COVID-19 was conducted by a group of long haulers *(patient.research.covid19@gmail.com)*.

- 80% of the people were between the ages of 30 and 60.

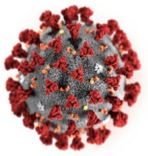
- The majority (54%) reported symptoms that had lasted **at least 3 months** since the start of the illness.

- Many had sought medical attention for these ongoing symptoms: **41% reported that the doctors had not listened to or believed them.**

50 Most Common Long Hauler Symptoms



NON-HOSPITALIZED COVID-19 AT 2-3 WKS

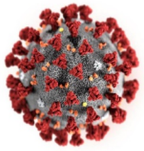


During April 15–June 25, 2020, telephone interviews were conducted with a random sample of adults aged ≥18 years who had a first **positive (RT-PCR) test for SARS-CoV-2, at an outpatient visit** at one of 14 U.S. academic health care systems in 13 states. There were 292 respondents. Interviews were **14–21 days after the test date**.

- 94% (274) reported one or more symptoms at the time of testing
- **35%** of these symptomatic respondents reported not having returned to their usual state of health by the date of the interview (median = 16 days)
  - 26% among those aged 18–34 years
  - 32% among those aged 35–49 years
  - 47% among those aged ≥50 years.
- Among respondents reporting **cough, fatigue, or shortness of breath** at the time of testing, 43%, 35%, and 29%, respectively, continued to experience these symptoms at the time of the interview.

Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States. Tenforde MW, et al. March–June 2020. MMWR Morb Mortal Wkly Rep 2020;69:993-998. DOI: http://dx.doi.org/10.15585/mmwr.mm6930e1external icon.

POST-HOSPITALIZED COVID-19 AT 60 DAYS



Patients were offered a comprehensive medical assessment with detailed history and physical examination. Data on all clinical characteristics, including clinical and pharmacological history, lifestyle factors, vaccination status, and body measurements, were collected in a structured electronic data collection system.

- Mean 60.3 (SD, 13.6) days after onset of the first COVID-19 symptom.
- No patients had fever or any signs or symptoms of acute illness.

- **Only 18 (12.6%) were completely free of any COVID-19–related symptoms**
- 32% had 1 or 2 symptoms
- 55% had 3 or more
- 44.1% observed worsened quality of life

- **Fatigue (53.1%),**
- **Dyspnea (43.4%)**
- **Joint pain (27.3%)**
- **Chest pain (21.7%)**

Persistent Symptoms in Patients After Acute COVID-19. Angelo Carfì et al. Research Letter. July 9, 2020. JAMA. 2020;324(6):603-605. doi:10.1001/jama.2020.12603

From: **Persistent Symptoms in Patients After Acute COVID-19**

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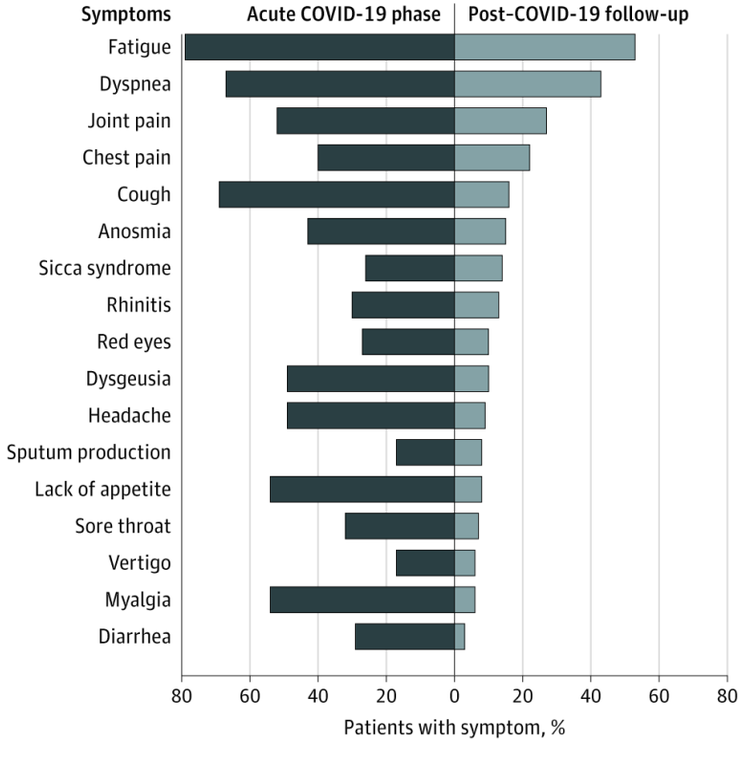
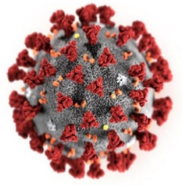


Figure Legend:

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).

WHAT DO POST-VIRAL SYNDROMES HAVE TO DO WITH COVID-19?



COVID-19: We are observing after the acute infection resolves, that many "long haulers" are still struggling with chronic multisystem illness manifestations.

It is too early to tell how much comes from the acute viral infection/inflammation, and how much is the development of a chronic post-viral syndrome.

Common post-COVID-19 chronic sequela

- Fatigue, sleepiness and brain fog/cognitive complaints
- Musculoskeletal issues, pain, headaches
- Respiratory tract inflammation
- Heart inflammation: myocarditis, pericarditis, chest pains, palpitations
- Neurologic symptoms: dizziness, headache, confusion, loss of smell and taste, altered consciousness, sleep disturbances
- Hair thinning and others

TABLE I: **SOME WELL-DESCRIBED POST-INFECTIOUS DISORDERS AND THEIR CAUSATIVE AGENTS (1988)**

- **Aplastic anemia**: Non-A, Non-B hepatitis
- **Arthritis:** Shigella, salmonella, yersinia, campylobacter, meningococcus, rubella, mumps
- **Encephalitis:** Measles, varicella, influenza, rubella, vaccinia (smallpox vaccination), rabbit brain or duck embryo rabies vaccines
- **Erythemas:** Tuberculosis, leprosy, yersinia, herpes simplex, hepatitis B
- **Glomerulonephritis**: Streptococcus pyogenes, hepatitis B, mumps
- **Guillain-Barre Syndrome**: Cytomegalovirus, Epstein-Barr virus, hepatitis A, hepatitis B
- **Auto-immune:** Syphilis, Mycoplasma pneumoniae
  - **Hemolysis and cytopenias**: Many common viral infections
- **Hemolytic uremic syndrome:** Escherichia coli
- **Reiter's syndrome:** Non-specific genital infection or bowel infections
- **Rheumatic fever:** Streptococcus pyogenes
- **Serositis**: Meningococcus

***vaccines *antimicrobials**

Post-infectious disease syndrome. B A Bannister. Review Postgrad Med J. 1988 Jul;64(753):559-67. doi: 10.1136/pgmj.64.753.559. PMID: 3074289 PMCID: PMC2428896 DOI: 10.1136/pgmj.64.753.559 Free PMC article

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POST STREPTOCOCCAL DISORDERS

- Acute rheumatic fever
- Acute glomerulonephritis
- Sydenham's Chorea
- PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders)
  - OCD, tics/myoclonus

Less common due to rapid testing and treatment options.

Post-Streptococcal Autoimmune Sequelae: Rheumatic Fever and Beyond. Madeleine W. Cunningham, PhD. Streptococcus pyogenes : Basic Biology to Clinical Manifestations [Internet]. Created: February 10, 2016. https://www.ncbi.nlm.nih.gov/books/NBK333434/

POST-VIRAL FATIGUE SYNDROME (PVFS)

Examples of viral Infections associated with chronic symptoms:

- **Herpes family viruses-**--After primary infection, remain latent. Chronic reactivating patterns are well known, particularly in immunocompromised patients.

- **Human parvovirus B19**
- **WNV and other flaviviruses**

- **Coronaviruses**
  - SARS CoV1
  - MERS
  - SARS CoV2

ICD-10 G93.3 PVFS

HERPES FAMILY VIRUSES

Herpesviruses establish latent infection within specific tissues, characteristic for each virus, and can reactivate. There are 100 known herpesviruses.

- **8 herpes viruses thAT routinely infect humans**
  - herpes simplex virus types 1 and 2 (**HSV**) *antivirals
  - varicella-zoster virus (**VZV**) *vaccine
  - cytomegalovirus (**CMV**)
  - Epstein-Barr virus (**EBV**)
  - human herpesvirus 6 (**HHV-6A and HHV-6 B**)
  - human herpesvirus 7 (**HHV-7**)
  - human herpesvirus 8 (Kaposi's sarcoma virus) (**HHV-8**)

Medical Microbiology: 4th Edition. Chapter 68. Richard J Whitley. 1996. . ViPR (Virus Pathogen Resource). www.viprbrc.org/brc/home.spg?decorator=vipr . Herpesviridae home page: www.viprbrc.org/brc/home.spg?decorator=herpes

ONE PROSPECTIVE STUDY OF PVFS

- Glandular fever (Epstein-Barr Virus)
- Epidemic polyarthritis (Ross River virus)
- Q-fever (Coxiella Burnetii)

Prospective cohort study: 253 patients with acute infection were enrolled and followed at regular intervals over 12 months by self report, structured interview, and clinical assessment.

Prolonged illness characterized by **disabling fatigue, musculoskeletal pain, neurocognitive difficulties, and mood disturbance** was evident in 29 (12%) of 253 participants at six months, of whom 28 **(11%) met the diagnostic criteria for chronic fatigue syndrome.** This post-infective fatigue syndrome phenotype was stereotyped and occurred at a similar incidence after each infection. The syndrome was predicted largely by the severity of the acute illness rather than by demographic, psychological, or microbiological factors

Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. Ian Hickie, Tracey Davenport, Denis Wakefield, Ute Vollmer-Conna, Barbara Cameron, Suzanne D Vernon, William C Reeves, Andrew Lloyd, for the Dubbo Infection Outcomes Study Group. BMJ, doi:10.1136/bmj.38933.585764.AE (September 2006)

WEST NILE VIRUS

- **40% of study participants (initial N=144) continued to experience symptoms related to their WNV infection up to 8 years later.**

- The most commonly patient-reported sequelae were **fatigue, weakness, depression, difficulty walking and/or feeling off balance, and memory loss.** Paralysis was reported by 9% of study participants, followed by tremors (5%) and seizures (1%).
  - **Two years** following infection, 47% (44/94) were still reporting symptoms, with the most commonly reported complaints being fatigue, weakness, difficulty walking, depression, and memory loss; 4% of study participants were still reporting paralysis.
  - **After five years**, 40% (29/73) were still reporting continued symptoms, with 26% of participants reporting depression.
  - **By eight years post-infection**, 40% (18/45) were still reporting WNV-related sequelae, with fatigue, depression, weakness, and neck/back pain most commonly reported.

Survival Analysis, Long-Term Outcomes, and Percentage of Recovery up to 8 Years Post-Infection among the Houston West Nile Virus Cohort. Kristy O. Murray, Melissa N. Garcia, Mohammad H. Rahbar, Diana Martinez, Salma A. Khuwaja, Raouf R. Arafat, and Susan Rossmann . PLoS One. 2014; 9(7): e102953. Published online 2014 Jul 23. doi: 10.1371/journal.pone.0102953. PMCID: PMC4108377 PMID: 25054656

West Nile Virus (WNV) chronic sequelae

- **Females, subjects < 50 years of age**, and those with **symptomatic clinical WNV disease** reported more fatigue.

- **Pro-inflammatory and antiviral cytokines** *(granulocyte macrophage colony stimulating factor, interferon-c, interferon-c inducing protein 10, interleukin 2, interleukin 6, and interleukin 12p70)* were significantly elevated in those reporting fatigue post-infection compared to those not reporting fatigue.

- **Clinicians should consider history of WNV infection as a possible factor when evaluating causes of prolonged fatigue following a febrile viral illness in their patients.** (flaviviruses: WNV, dengue, Zika, etc.)

Evaluation of Prolonged Fatigue Post–West Nile Virus Infection and Association of Fatigue with Elevated Antiviral and Proinflammatory Cytokines. Melissa N. Garcia, Anne M. Hause, Christopher M. Walker, Jordan S. Orange, Rodrigo Hasbun, and Kristy O. Murray. Viral Immunol. 2014 Sep 1; 27(7): 327–333. doi: 10.1089/vim.2014.0035. PMCID: PMC4150370. PMID: 25062274

CORONAVIRUS: SARS COV-1

A province-wide emergency was declared on March 26th, 2003 in Toronto, Canada. 3 months later **273 people had been identified as confirmed SARS cases. 44 died.**

22 Toronto subjects, 21 of whom were healthcare workers, (19 females, 3 males, mean age 46.29 yrs.+/- 11.02), who remained **unable to return to their former occupation (mean 19.8 months, range: 13 to 36 months following SARS**) due to sleep physiology, somatic, and mood symptoms were compared to 7 healthy female subjects, and 21 FM patients.

On most days Post-SARS subjects complained of tiredness, difficulty sleeping, myalgia and muscular weakness.

Compared to healthy controls, Post SARS subjects had more:

- Mild to moderate depressive symptoms (BDI mean = 13.3 +/- 8 vs.0.86 +/- 1.5, $p < .0001$)
- Sleep disturbances on the SAQc (mean total score = 30.9 +/- 5 vs. 10.9 +/- 3.4, $p < .0001$)
- Fatigue post-sleep ($p < .05$)
- Myalgia pre- and post-sleep ($p < .01$)

Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. Harvey Moldofsky and John Patcai. BMC Neurol. 2011; 11: 37. Published online 2011 Mar 24. doi: 10.1186/1471-2377-11-37. PMCID: PMC3071317. PMID: 21435231

(ME/CFS)
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

- A chronic, debilitating, multisystem illness characterized by **central and peripheral nervous system disease, immune manifestations, and impaired cellular metabolism**.

- ME/CFS is thought to be a post-viral or post-infection syndrome in most, but not all, cases.

HOW IS ME/CFS TRIGGERED?

150 ME/CFS patients *queried by detailed survey reported the following factors to be associated with their ME/CFS onset. (Table 1)*

Onset Factor	No. of subjects	% of subjects
Infectious illness	**84**	**64**
Stress or major life events	**51**	**39**
Exposure to chemical/environ/toxins	26	20
Recent international travel	25	19
Recent domestic travel	23	17
Other…	22	17

Onset Patterns and Course of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Lily Chu, et al. Front Pediatr. 2019; 7: 12. doi: 10.3389/fped.2019.00012. PMCID: PMC6370741. PMID: 30805319

HOW IS ME/CFS TRIGGERED?

Subject-reported infectious events related to ME/CFS-onset.

Type of infection	No. of subjects	(%)
Respiratory infection (sore throat, runny nose, cough, etc.)	33	39
Documented acute infection (herpes viruses, parvoB19, etc.)	29	35
Non-specific infection (fever, chills, sweats, myalgia)	28	33
Other…	15	18
Abdominal infection (diarrhea, nausea, vomiting)	10	12

Onset Patterns and Course of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Lily Chu, et al. Front Pediatr. 2019; 7: 12. doi: 10.3389/fped.2019.00012. PMCID: PMC6370741. PMID: 30805319

ME/CFS CAN BE TRIGGERED BY A VARIETY OF PATHOGENS

- Many viral infections are capable of causing a postviral syndrome; and a number have been associated with the development of ME/CFS, including **Epstein-Barr Virus, other herpesviruses, Parvovirus B19, West Nile Virus, enteroviruses, and other non-viral pathogens as well.**

- ME/CFS may be caused by the body's complex reactions to certain infections in combination with **an abnormal chronic immune/inflammatory response**.

- People with ME/CFS share the same core symptoms but heterogeneity exists, likely due to the systems affected, disease duration and the development of comorbid conditions. This heterogeneous illness is challenging to study.

ME/CFS 2015 CLINICAL DIAGNOSTIC CRITERIA

CORE criteria (required for diagnosis)

*Must be moderate-severe and present >50% of time

1) **Impairment of normal function accompanied by fatigue, >6 months**
2) **PEM: post exertional malaise***
3) **Unrefreshing sleep***
4) Plus at least one of the following:

   Cognitive impairment*

   Orthostatic intolerance (autonomic nervous system dysregulation)

Additional common but not "CORE" features of illness in the ME/CFS population:

- **Chronic pain** (headache, muscle and joint aches, hyperalgesia, central sensitivity, tingling, burning, etc.)
- **Immune/inflammatory manifestations** (allergy, inflammation, immunodeficiency, chemical sensitivities)
- **Infection manifestations** (viral or atypical infections, sore throat, tender lymph nodes, low grade fevers)
- **Neuroendocrine manifestations** (HPA-axis dysregulation, impaired stress response)

Beyond Myalgic Encephalomyelitis: Redefining an Illness. Institute of Medicine. Washington (DC): National Academies Press (US); 2015 Feb 10. ISBN-13: 978-0-309-31689-7ISBN-10: 0-309-31689-8

SELECTED COMMON CO-MORBID CONDITIONS OF INTEREST IN ME/CFS PATIENTS

- Fibromyalgia/pain amplification, central sensitivity
- Small fiber poly neuropathies (SFPN) and peripheral neuropathies
- Neuroinflammation in the brain
- Viral reactivation (VZV, HSV, HHV-6, EBV, CMV)
- Chronic sleep disorders ("primary" and otherwise)
- Postural orthostatic tachycardia syndrome (POTS), orthostatic hypotension, other dysautonomias
- Allergies, chemical sensitivities, mast-cell activation syndrome (MCAS), food intolerances
- Autoimmune thyroid disease, subclinical hypothyroidism, euthyroid-sick syndrome
- Celiac disease and gluten intolerance
- IBS, gastroparesis, SIBO (small intestine bacterial overgrowth)
- Sjogren syndrome/sicca syndrome (dry eyes and dry mouth)

A POSSIBLE ROLE FOR HHV-6 IN ME/CFS

- To understand possible causative role of HHV-6 in ME/CFS, metabolic and antiviral phenotypes of U2-OS cells were studied **with and without chromosomally integrated HHV-6** and **with or without virus reactivation** using the histone deacetylase inhibitor trichostatin-A.

- Reactivation of HHV-6 was shown to fragment mitochondria in vitro

- HHV-6 reactivation in ME/CFS patients activates a multisystem, proinflammatory, cell danger response that protects against certain RNA and DNA virus infections but comes at the cost of mitochondrial fragmentation and severely compromised energy metabolism.

Human Herpesvirus-6 Reactivation, Mitochondrial Fragmentation, and the Coordination of Antiviral and Metabolic Phenotypes in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Philipp Schreiner,* Thomas Harrer,† Carmen Scheibenbogen,‡ Stephanie Lamer,§ Andreas Schlosser,§ Robert K. Naviaux, and Bhupesh K. Prusty*,1- ImmunoHorizons 2020, 4 (4) 201-215. doi: https://doi.org/10.4049/immunohorizons.2000006

THE ROLE OF STRESS

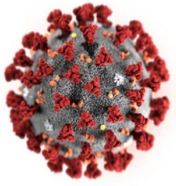
Lessons from NASA Space Program:

- 47/89 (53%) astronauts from shuttle-flights and 14/23 (61%) astronauts from ISS missions shed one or more herpes viruses in saliva/urine samples (detected by PCR).
  - Epstein–Barr virus (EBV), varicella-zoster virus (VZV), and herpes-simplex-1 (HSV-1) in saliva and cytomegalovirus (CMV) in urine.

- The hypothalamus-pituitary-adrenal (HPA) axis along with the sympathetic-adrenal-medullary (SAM) axis partially mediate the stress response where glucocorticoids and catecholamines are secreted in proportionate concentrations relative to the stress stimulus.

Herpes Virus Reactivation in Astronauts During Spaceflight and Its Application on Earth
Bridgette V. Rooney1, Brian E. Crucian2, Duane L. Pierson2, Mark L. Laudenslager3 and Satish K. Mehta4*Frontiers in Microbiology. REVIEW. published: 07 February 2019. doi: 10.3389/fmicb.2019.00016

WHAT DO PVFS AND ME/CFS HAVE TO DO WITH COVID-19?



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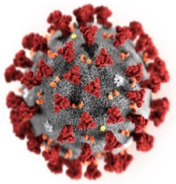
SARS-COV2: NEUROINVASIVE AND NEUROTROPIC



- Coronaviruses can enter the **central nervous system (CNS)** through hematogenous spread, or the **peripheral nervous system** through axonal transmission. The olfactory nerve, trigeminal nerve or the sensory fibers of the (PNS) vagus nerve are the most common peripheral nerve targets.

- SARS CoV2 can ACUTELY affect every system/tissue perfused by the vascular system (pulmonary, musculoskeletal, ocular, cardiovascular, gastrointestinal, urogenital, dermatologic…)

COVID-19 Guide for the Rehabilitation Clinician: A Review of Non-Pulmonary Manifestations and Complications. Marielisa Lopez, et al Am J Phys Med Rehabil. 2020 May 26 : doi: 10.1097/PHM.0000000000001479. PMCID: PMC7299122. PMID: 32467492.

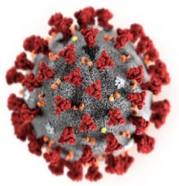
COVID-19 NEUROPSYCHIATRIC PATHOLOGY

Potential mechanisms

- Viral infiltration into the CNS
- Cytokine network dysregulation
- Peripheral immune cell transmigration
- Post infectious autoimmunity/neuroimmune
- Gut microbial translocation

Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. Review Brain Behav Immun. 2020 Jul;87:34-39. doi: 10.1016/j.bbi.2020.04.027. Epub 2020 Apr 13. Emily A Troyer, etal. PMID: 32298803 PMCID: PMC7152874 DOI: 10.1016/j.bbi.2020.04.027. Free PMC article

COVID-19: LYMPH NODES AND SPLEEN



The spleens and lymph nodes of deceased COVID-19 patients were examined, and a lack of germinal centers was found-an essential part of a durable immune response.

In lymph nodes and spleens in acute COVID-19 there is a striking loss of germinal centers, **depletion of Bcl-6+ B cells** but preservation of AID+ B cells.

A specific block in germinal center type **Bcl-6+ T follicular helper cell** differentiation explains the loss of germinal centers and the accumulation of non-germinal center derived activated B cells.

This data provides a mechanism for the lower quality and lack of durability of humoral immune responses observed during natural infection with SARS-CoV-2 and have significant implications for expectations of herd immunity.

PREPRINT: The loss of Bcl-6 expressing T follicular helper cells and the absence of germinal centers in COVID-19. Naoki Kaneko… Shiv Pillai1# and the Massachusetts Consortium on Pathogen Readiness Specimen Working Group. https://ssrn.com/abstract=3652322

WE OFTEN MISS MORE "INVISIBLE" CONDITIONS

- Neuroinflammation
- Small fiber neuropathy
- Autoantibodies not routinely measured clinically
- Nonspecific immune dysregulation
- Chronic inflammation w/o elevated ESR or CRP

WHY DOES IT MATTER?

- In medicine **we focus on acute infections** and are **generally unfamiliar with post-viral syndromes**, especially those that do not resolve in a few weeks.
- People recovering from COVID-19, in addition to suffering from the many systems targeted by the virus, have been victims of **insufficient medical resources, huge uncertainty/fear, and unprecedented isolation and loneliness.**
- Not feeling "believed" when experiencing debilitating illness symptoms is a crushing and destabilizing experience emotionally. **Some physiologic symptoms can also be misdiagnosed as anxiety or depression.**
- Recognizing **a pattern of post-viral illness**, especially if there are known criteria and supportive treatment approaches, is empowering and restores some control.
- **Early intervention may improve long term prognosis.**

WHAT CAN COVID-19 TEACH US ABOUT POST-INFECTIOUS FATIGUE SYNDROMES AND ME/CFS?

- It is likely that the causes of **post-infectious fatigue syndromes** and **ME/CFS** share many similarities. **It is quite possible that longitudinal studies of people who develop COVID-19 can help reveal the causes of these illnesses.**

- **Longitudinal studies of SARS CoV2 infections** must be done to assess:
  - The presence and severity of symptoms - symptoms common in people with COVID-19 and that are part of case definitions of ME/CFS and PVFS.
  - Laboratory studies of the immune system, metabolism, gene structure and expression.
  - As well as tests of cognition, sleep, and the functioning of the brain and nervous system, heart and cardiovascular system.

US ME/CFS Clinician Coalition. Consensus letter, publication pending.