About the Patient-Generated Hypotheses Journal

Welcome to the Patient-Led Research Collaborative's first issue of the Patient-Generated Hypotheses Journal. This issue is a compilation of six hypotheses plus poll results. People with Long COVID and associated conditions and caregivers of people with these conditions developed, wrote, chose, and edited this issue.

Historically, biomedical research has prioritized hypotheses developed by researchers without lived experience of the conditions they study. People with lived experience who have hypotheses about the mechanisms of their conditions did not have a platform to share their hypotheses, except for within patient communities.

Centering patient expertise

At the Patient-Led Research Collaborative (PLRC), we have put patients in the driver's seat of research since April 2020. We centered patients in sourcing hypotheses for Long COVID in the development of our own surveys[1], in choosing what research to fund[2], and in setting a new baseline for meaningful patient engagement[3]. We know that patients are the foremost experts on their own bodies. We also know that many patients are immersed in research in areas that the majority of the medical community has yet to explore.

The authors of this issue are from diverse professional and academic backgrounds, ranging from self-taught to Ph.D. One of the goals of our Patient-Generated Hypotheses Journal is to highlight the immense talent pool of our patient network, from their backgrounds, their lived experience of being a patient or caregiver, and from their ability to synthesize existing research and align it with their own hypotheses. Additionally, patients and caregivers are often communicating with each other online, discussing symptoms, experiences, lab results, and the reactions to various medications they are trying. This pattern recognition is invaluable and regularly results in patients identifying discoveries well before the public and the medical community.

Structure and aims of the journal

We have seen first-hand that patient-led research is more effective, timely, accessible, and representative, in addition to prioritizing topics that are most important to the patient community. With that in mind, PLRC developed the Patient-Generated Hypotheses Journal. First, we created a panel of patient-researchers with lived experience of Long COVID, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and other associated conditions[4]. Then we created the process outlined in Figure 1. The process includes determining criteria and format of hypotheses, crowdsourcing submissions, selecting based on strength of evidence, reviewing and editing chosen hypotheses, assembling into this publication, and submitting to an open science journal.

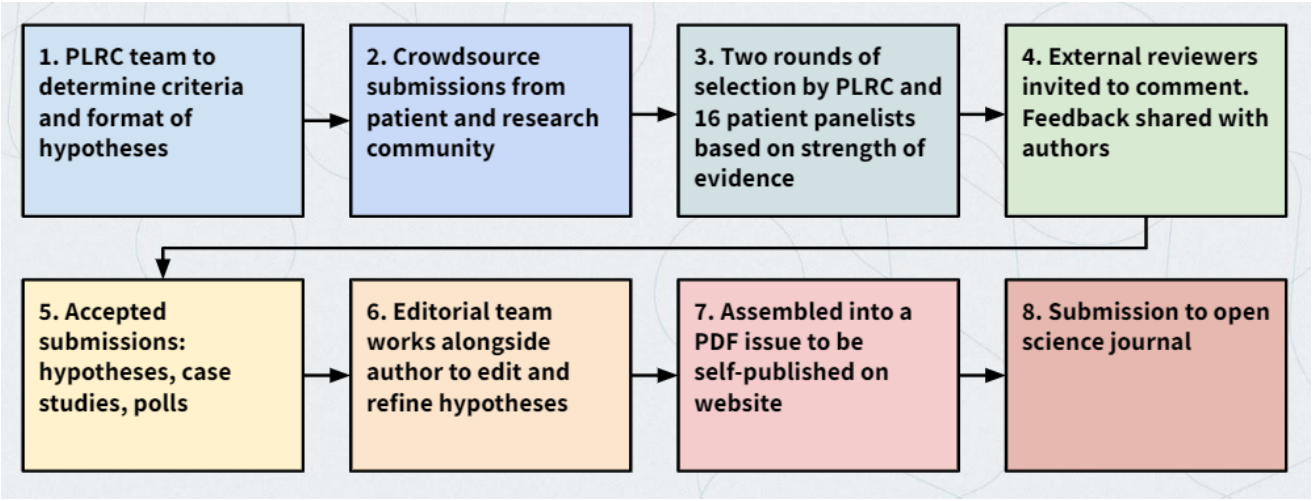

Figure 1. *Patient-Generated Hypotheses Process*

Each hypothesis has an abstract that gives an easy-to-read summary, followed by the in-depth hypothesis with supporting evidence. Most of the entries also provide instructions for how to test the hypothesis, and all highlight unanswered questions.

The hope is for biomedical researchers to use these hypotheses as inspiration for their research, to partner with the author and other patients/caregivers in testing the hypothesis, and to uplift patient-generated hypotheses as a credible source of research generation.

By giving the patient community a platform and voice in the research process, we anticipate new discoveries and better outcomes for people with chronic illnesses.

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Table of contents

Hypothesis

Long COVID brain fog is caused by free glycan sugar chains in the brain

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Abstract

Coronavirus spike proteins are composed of glycoproteins, molecules that have a protein center and sugar side-chains. These coronavirus glycans interact with other protein-sugar molecules present on the outer surface of cells, known as the glycocalyx. Coronavirus spike proteins particularly interact with the glycocalyx within blood vessels, causing these protein-sugars to peel off the internal walls of blood vessels. Previous work has shown that during sepsis, protein-sugar molecules similarly slough off the internal walls of blood vessels, cross the blood-brain barrier and contribute to cognitive, memory, and mood disorders. This proposal hypothesizes that viral persistence and constant coronavirus spike protein presence in the bloodstream of Long COVID patients similarly causes an ongoing degradation of endothelial glycocalyx, resulting in free floating glycan sugar side-chains that contribute to the cognitive issues observed in this condition.

Introduction

Proteoglycans are a broad group of molecules, comprised of a core protein surrounded by sugar side-chains that are composed of differentially sulphated groups of glycosaminoglycans (GAG); both the core protein and sugar chains determine binding affinity and functionality of a proteoglycan[1,2]. The spike proteins found on the external surface of SARS-CoV-2, the virus that causes COVID-19, are glycoproteins, also composed of a protein core and sugar side-chains[3-5]. During normal function, sugar side-chains are constrained to their core proteins and do not interfere with normal biological processes; however, free glycan side-chains can damage various tissues, such as during sepsis[6-8].

These glycan fragments are small enough to pass the blood-brain barrier, resulting in impaired memory and cognitive functions both during and after sepsis, thought to be due to the presence of free glycan side-chains within the brain[6,7]. The SARS-CoV-2 proteoglycan spike protein is known to persistently circulate in patients with Long COVID[10], and is known to both cross and disrupt the function of the

blood-brain barrier[11-13]. This proposal addresses the possibility that freely circulating, persistent SARS-CoV-2 spike protein is a major contributor to the cognitive and memory deficits experienced by patients with Long COVID.

Hypothesis

Proteoglycans play many different roles in cellular and biological processes, particularly heparan sulfate proteoglycans (HSPGs)[2] like those thought to act as a co-receptor for the SARS-CoV-2 virus[3-5]. HSPGs mediate growth factor signaling, provide guidance during cellular migration and axonal growth within the brain, organize the extracellular matrix, enable cellular motility and adhesion, and facilitate virus-host interactions among other cell-cell crosstalk[2]. HSPGs may be secreted into and participate in the extracellular matrix, form intracellular secretory vesicles, or be bound to cellular membranes[2], where they act as co-receptors for various growth factors, proteins and the SARS-CoV-2 virus[3-5].

Proteoglycans and glycoproteins within the brain regulate neuronal health, form chemical gradients that guide cellular migration during development, provide cellular support, enable synaptic connections, regulate the availability and signaling of growth factors, and close off critical periods by helping to solidify mature neural networks[2, 14-18]. It has been seen that altering proteoglycans within the rodent brain results in altered behavior[19-21] and neural function[22,23].

Recent work has established the presence of free-floating SARS-CoV-2 spike protein within the blood of Long COVID patients[8]. It is hypothesized that viral persistence within patients results in a variety of immunological, neurological, and autonomic dysregulation, while also providing a constant supply of the spike glycoprotein. The presence of freely circulating glycans has also been detected, and significantly contributes to pathophysiology during sepsis[6,7]. Like Long COVID, sepsis is a multi-organ, multi-system inflammatory process where normal cellular activity is disrupted or completely breaks down, and the two have been compared as having similar long-term sequelae[35]. Proteoglycans and glycoproteins that are sloughed off blood vessel endothelia during sepsis are capable of crossing the blood-brain barrier, and are thought to contribute to the ongoing cognitive and neurological issues seen in post-sepsis syndrome[6-9]. Similarly, the free floating spike protein found in the blood of Long COVID patients is also capable of crossing the blood-brain barrier[12,13], and high levels of HSPGs have been found in the blood of COVID-19 patients due to endothelial glycocalyx disruption[3]. What is not known is whether the presence of these glycans in the brain contributes to the cognitive and neurological issues seen in Long COVID, similar to the effect observed in septic and post-septic patients.

This proposal puts forward the hypothesis that the circulating SARS-CoV-2 spike protein found in Long COVID patients crosses the blood-brain barrier and interferes with normal neuronal and cellular functioning within the brain, contributing to the brain fog, speech impediments, memory issues,

cognitive impairments, and other neurological disorders observed in patients with Long COVID.

How to test the hypothesis

Assessing patient tissue

- Assess proteoglycan and glycoprotein sugar side-chain recovery from post-mortem tissue taken from the brains of severe acute COVID-19 patients. Recover glycan chains and perform liquid chromatography mass spectrometry using established techniques[7] to assess the presence of the SARS-CoV-2 spike protein or free-floating HSPG sugar side-chains within various brain regions.
- Correlate circulating glycan levels with brain glycan measurements and behavioral/cognitive performance to determine how free floating SARS-CoV-2 spike protein and elevated HSPG blood levels correlate with impaired cognitive capabilities.

Assessing animal studies

- Use an established Long COVID animal model such as that published by Frere et al. (2022)[30]. Compare behavioral performance in the Puzzle-Box to assess cognitive capabilities[29] across a Long COVID animal model, sepsis animal model, and possibly animal model with disturbed brain glycans (i.e. chondroitinase and heparinase injections into the hippocampus).
- Fresh frozen brains from the above animals: recover glycan chains and perform liquid chromatography mass spectrometry[7] to assess the presence of the SARS-CoV-2 spike protein and free-floating HSPG sugar. side-chains within various brain regions. Stain brain samples for 3G10 and 10EF to assess the presence of broken/free floating proteoglycan side-chains versus bound/complete side-chains[27], and for perineuronal nets using wisteria floribunda agglutinin (WFA) to assess the state of the glycans within the brain extracellular matrix[28].
- Collect trunk blood at sac: process for the presence of free floating proteoglycans and glycoproteins, including the SARS-CoV-2 spike protein.
- Correlate circulating glycan levels with brain glycan measurements and behavioral performance to determine how much free floating glycans, including the SARS-CoV-2 spike protein, contribute to impaired cognitive capabilities.

Potential therapeutics

- Nattokinase to dissolve persistent circulating SARS-CoV-2 spike protein[31]
- Synthetic heparan sulfate mimetics to disrupt glycocalyx degradation caused by persistent SARS-CoV-2 spike protein[32]
- Drugs used to restore endothelial functioning in diabetes treatment[33,34]

Unanswered questions

1. Do Long COVID patients have ongoing endothelial glycocalyx degradation similar to that observed in acute COVID patients?

2. What neurological or cognitive impacts do the free-floating SARS-CoV-2 spike protein glycans have in patients with Long COVID?

3. How can we measure or determine this?

4. What are some ways in which we can eliminate the free floating glycans from Long COVID patients' tissues, particularly within the brain?

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Hypothesis

Symptomatic myodesopsia/vitreous floaters may constitute a risk factor for Long COVID and ME/CFS

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Abstract

The ophthalmological condition known as myodesopsia or vitreous floaters results from aggregates of proteins or cellular debris in the vitreous body casting shadows onto the retina that are perceived as objects moving through the visual field. While this is commonly viewed as a benign condition associated with aging, a growing body of research suggests that for some patients it can severely impact visual function and quality of life. Myodesopsia is often caused by posterior vitreous detachment, but can also result from other conditions such as asteroid hyalosis, uveitis, or myopic vitreopathy. There are strong reasons to suspect that its presence may be indicative of a susceptibility to collagen degradation in response to inflammatory triggers, which may represent a risk factor for the development of Long COVID, ME/CFS, or related chronic illnesses. Evidence for such susceptibility includes the presence of collagen-degrading enzymes in the vitreous, associations with other connective tissue disorders, and links between myodesopsia and infections with various pathogens.

Introduction

Myodesopsia, also known as vitreous floaters or "eye floaters," is an ophthalmological condition in which aggregations of proteins or other cellular debris within the vitreous body, the normally transparent gel that occupies the space between the retina and lens, cast shadows onto the retina that are perceived as objects moving through the visual field[1]. Clinicians have traditionally viewed myodesopsia as a common and mostly benign phenomenon associated with normal aging that only causes significant disability or morbidity very rarely, if at all[2]. A growing body of research has shown, however, that for a subset of patients the impact on visual function and quality of life can be severe[3,4,5,6].

In older adults, the leading cause of myodesopsia is an age-related development known as posterior vitreous detachment (PVD), which occurs when the vitreous undergoes collapse and detaches from the retina due to progressive liquefaction of its gel structure. Symptomatic floaters are often found in younger individuals as well though, even if their exact prevalence has not been established. In patients without PVD, floaters may result from conditions such as asteroid hyalosis, uveitis, or, more commonly, myopic vitreopathy[7].

Although the precise etiological mechanisms behind myodesopsia in many instances remain unknown - and the condition is often therefore deemed "idiopathic"—there are strong reasons to suspect that such cases may be indicative of a susceptibility to collagen degradation in response to inflammatory triggers. This in turn may represent a risk factor for the development of Long COVID, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), or related chronic illnesses. There is evidence that collagen breakdown may be a significant factor in these diseases insofar as it is a correlate of damage to structurally important connective tissues, such as the ligaments of the craniocervical junction[8].

Hypothesis

We review here three reasons why floaters may be a sign of vulnerability to such breakdown.

First, collagen-degrading enzymes are present in human vitreous and are likely involved in structural changes thereto. The vitreous is an extracellular matrix (ECM) that consists of roughly 98% water and 2% structural macromolecules, chief among them hyaluronan and collagen (including types II, IX, and a hybrid of types V and XI)[7]. It also contains varying concentrations of matrix metalloproteinases (MMPs), proteolytic enzymes that are believed to play a role in age-related vitreous liquefaction[9]. These include MMP-1 (interstitial collagenase), MMP-2 (gelatinase A), MMP-3 (stromelysin-1), and MMP-9 (gelatinase B)[10]. Indeed, pharmacological inhibitors of MMP activity have been proposed as candidates for prophylaxis of vision-degrading myodesopsia[7]. An implication is that symptomatic floaters in younger patients could be evidence of a greater-than-ordinary propensity to MMP upregulation and collagen breakdown, including in response to infection.

Second, myodesopsia has been identified as a comorbidity in other connective tissue disorders, some of which themselves potentially increase risk for the development of Long COVID and ME/CFS[11]. Sebag (2014) describes known associations with Marfan syndrome and Ehlers-Danlos syndrome (EDS)[12]. Milhorat et al. (1999) note that "floaters or flashing lights" were reported by 200 out of 364 patients (54.9%) with a diagnosis of Chiari I malformation or syringomyelia[13]. (To put this figure in context, one 2021 survey of ophthalmologists and optometrists found that "only" between 17% and 32% of all patients reporting to the typical clinic for an ocular examination have some amount of symptomatic floaters[14].) In a 2013 lecture on cervical medullary syndrome, which involves structural compression of the brainstem, Dr. Roger Kula

explicitly hypothesized that the high prevalence of floaters in this patient population was due to a correspondingly high predisposition for connective tissue disorders (see at 17:00 in the cited recording)[15].

Third, there are known links between myodesopsia and infection with various pathogens, such as Borrelia[16], Bartonella[17], and Toxoplasma[18], suggesting that the presence of floaters may be evidence of a prior collagen-degrading infectious process even when a specific causative agent cannot be identified. Floaters have already been highlighted in the literature as a possible ocular sequela of COVID-19 itself[19], and online forums and support groups for myodesopsia sufferers are now filled with anecdotal reports of onset following SARS-CoV-2 infection or even COVID vaccination(see the appendix for a sampling of recent anonymized reports of floater onset following SARS-CoV-2 infection or vaccination from the Reddit communities r/CovidLongHaulers and r/EyeFloaters, which currently have over 45,000 and 6,000 members, respectively)[20,21].

How to test the hypothesis

Testing this hypothesis would ideally entail conducting a well-powered prospective longitudinal study in which individuals with and without symptomatic myodesopsia would be followed for a period of time so that the incidence of Long COVID or ME/CFS in both groups could be ascertained. For study purposes, a diagnostic definition of myodesopsia should be adopted that incorporates both patients' own symptom reports as well as objective clinical indicators like contrast sensitivity function and vitreous echodensity as measured by quantitative ultrasound[22]. If the hypothesis is correct, it would suggest that a relatively simple ocular screening might be a cost-effective way of identifying at least one subset of patients at higher risk for these serious conditions. It would also provide an additional rationale for performing genetic studies aimed at uncovering as yet unknown mutations associated with a tendency to developing them, which could in the future enable a more targeted approach to prevention of myodesopsia as well as of various complex chronic illnesses.

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Appendix: Anonymized anecdotal reports of myodesopsia onset following SARS-CoV-2 infection or COVID vaccination from online communities

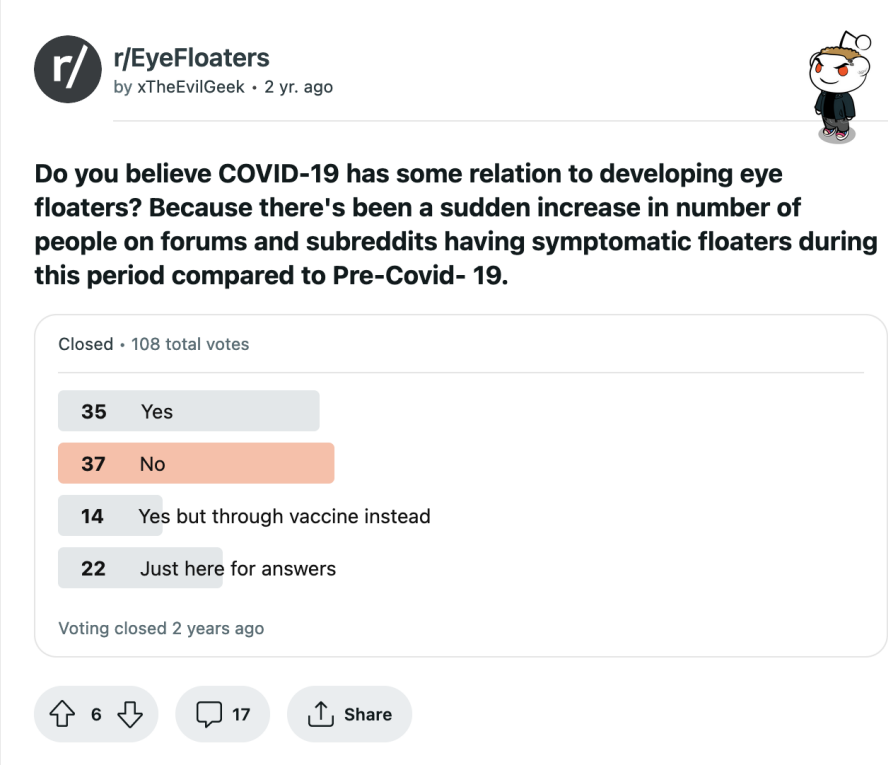

Figure 1. *Poll from the Reddit community r/EyeFloaters on the relationship between COVID and developing eye floaters. Source: https://www.reddit.com/r/EyeFloaters/comments/qhtek3/do_you_believe_covid19_has_some_relation_to/*

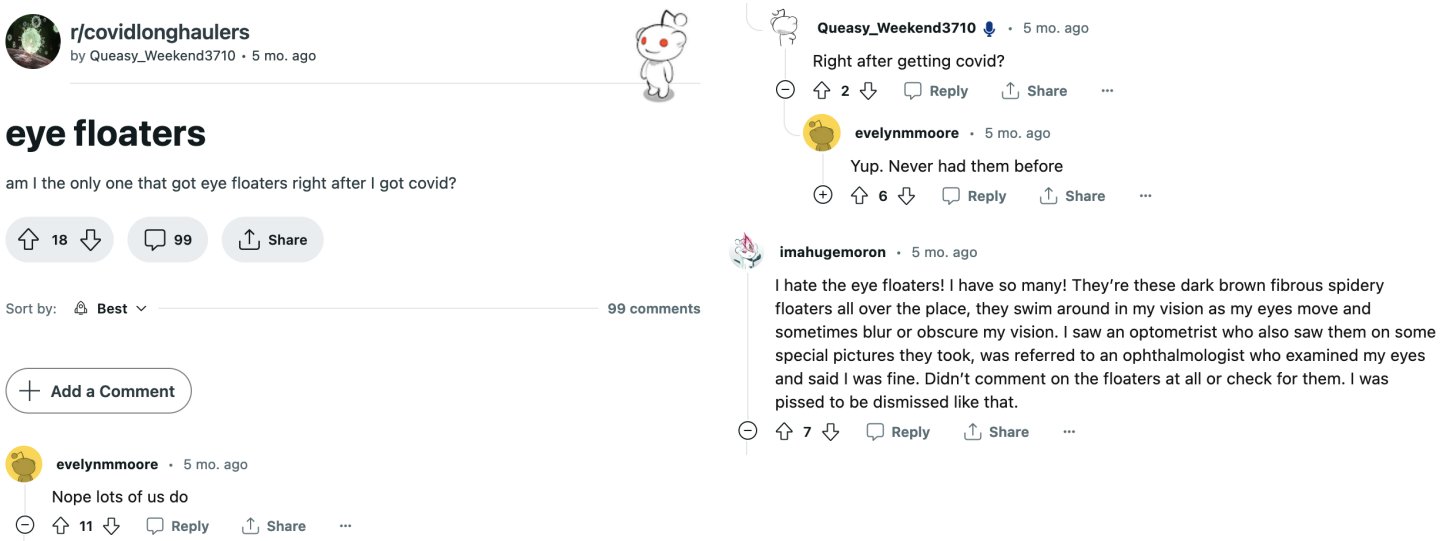

Figure 2.1, 2.2. *Post from the Reddit community r/covidlonghaulers on eye floaters after COVID. Source: https://www.reddit.com/r/covidlonghaulers/comments/zt6nc4/eye_floaters/*

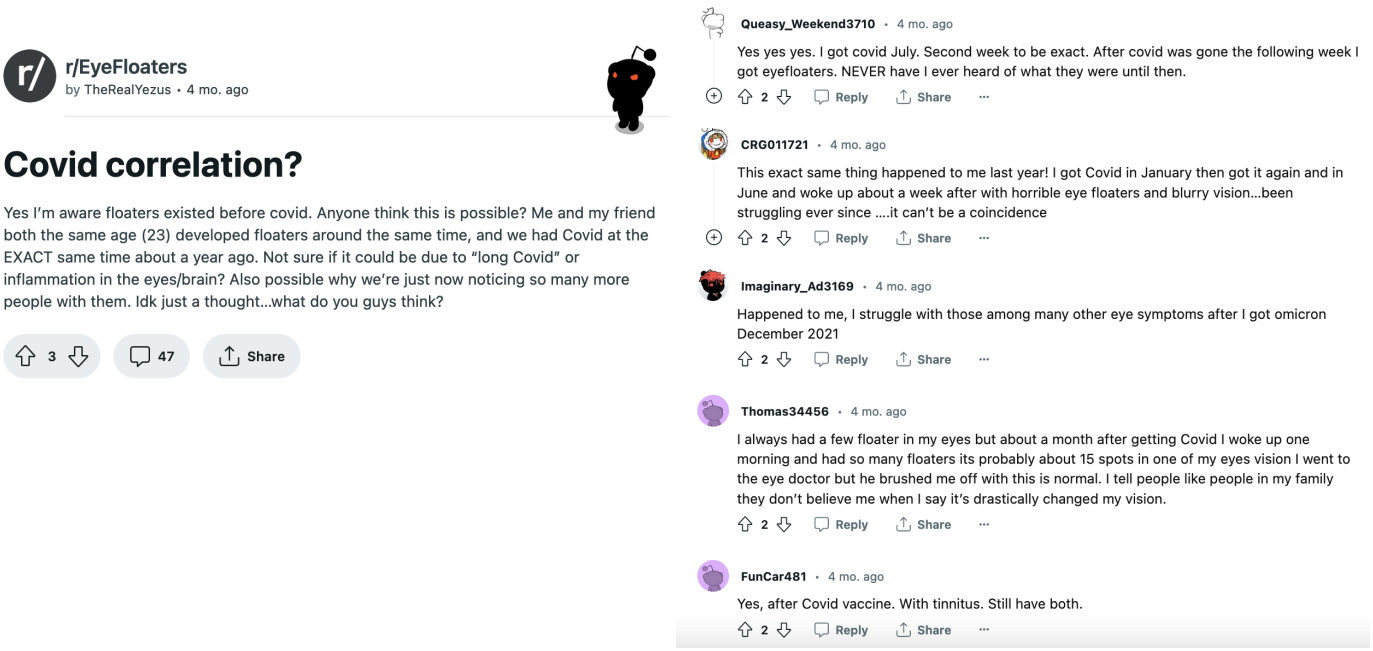

Figure 3.1, 3.2. *Post from the Reddit community r/EyeFloaters on COVID Correlation. Source: https://www.reddit.com/r/EyeFloaters/comments/1068b8v/covid_correlation/*

Figure 4. *Post from the Reddit community r/EyeFloaters on floaters after COVID vaccine. Source: https://www.reddit.com/r/EyeFloaters/comments/pl013m/floaters_after_covid_vaccine/*

Hypothesis

Matrix metalloproteinase inhibition with low-dose doxycycline in Long COVID and ME/CFS

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Abstract

Nonselective matrix metalloproteinase (MMP) inhibition with FDA approved subantimicrobial dose doxycycline formulations could improve systemic symptoms in at least a subset of patients with Long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) as compared to those who receive placebo.

Hypothesis

The chronic inflammatory state induced by Long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) likely increases systemic collagenase activity, causing pathologic collagen breakdown and loss of tissue structural support. A cascade of symptomatology across organ systems could follow, including those stemming from increased tissue laxity and distention, as well as increased permeability of important tight junctions in mucosal barriers[1, 2], vasculature[3] and the blood-brain barrier[4, 5]. Existing subantimicrobial or low-dose doxycycline (LDD) formulations with established efficacy to inhibit matrix metalloproteinase (MMP) activity are worth exploring to stabilize symptoms in parallel to the development and trial of other therapeutics.

MMPs have been found to be elevated in patients with various infections and chronic illnesses[6, 7]. A recent study also showed that MMP-9 produced from cancer cells was able to induce remodeling of capillary endothelial cells and support early brain metastasis[8]. Similarly, studying the biomechanics of neuroinvasive pathogens that cause infectious diseases like COVID-19 and Lyme may help us better understand transport across the blood-brain barrier, seeding of infection, and persistence into the central nervous system (CNS)[9, 10]. Due to its ability to cross the blood-brain barrier, doxycycline has long been used as standard of care to treat Lyme disease,

including facial palsy, meningitis, or radiculoneuritis from neuroborreliosis in both adults and children[11]. Doxycycline has shown the ability to reduce neuroinflammation[12, 13], which is a leading hypothesis for the widespread neuropsychological symptoms observed in patients with Long COVID[14-16] and to a lesser extent in ME/CFS[17]. More generally, in addition to their antibiotic mechanism of action, the tetracycline class of antibiotics can induce immunomodulatory and anti-inflammatory activity in patients with autoimmune diseases[18]. Enzymes like MMPs that are secreted to degrade connective tissue are triggered by immune cell signaling, but are also a part of a feedback loop where subsequent tissue damage or breakdown provokes additional immune responses[19]. Immunomodulating therapies like LDD that inhibit MMPs have the potential to disrupt this inflammatory cycle, which may allow the tissues to heal. Despite the first tetracycline being discovered in 1948, the use of doxycycline for non-antibiotic indications has not been widely adopted in clinical practice[20]. Currently, only two LDD formulations have FDA approval with indications of periodontal disease (Periostat®[21]) and rosacea/acne (Oracea®[22]), granted in 2001[23] and 2006[24], respectively. For decades, many synthetic MMP inhibitors have shown remarkable potential in vivo and in vitro, but their translation into advanced clinical trials has largely failed due to musculoskeletal toxicity or lack of efficacy[25-27]. Fascinatingly, what has helped make doxycycline a clinically useful MMP inhibition therapy is its incomplete blockade, causing side effects to be less profound and overall more tolerable[28].

If chronic immune activation is contributing to endothelial dysfunction[29, 30], hypercoagulability, and fibrinaloid microclot formation[31, 32] already observed in patients with both Long COVID and ME/CFS, could it also compromise connective tissue integrity and the structural stability of critical joints that protect the nervous system? This process may partially explain why many patients receive comorbid diagnoses like mast cell activation syndrome (MCAS)[33, 34] and hypermobile Ehlers Danlos Syndrome (hEDS)[35, 36]. In fact, when researchers took the skin cells of patients with hEDS and treated them with doxycycline in vitro, the antibiotic restored extracellular matrix organization and significantly attenuated myofibroblast-like features[37]. This work shows that the cellular structural changes in hEDS have the potential to be reversible, and that doxycycline can modulate at least a part of that process. Growing literature is revealing the complex interplay of the extracellular matrix and the immune system[19], which may help to explain the overlap of connective tissue disorders like hEDS with Long COVID and ME/CFS. Importantly, treatment with LDD does not preclude the use of other medications utilized in tandem to help control chronic inflammatory responses like dual antihistamine blockade with or without mast cell stabilization to help prevent further tissue breakdown and aid in tissue repair[38]. Furthermore, clinical trials have shown LDD can be safely taken for up to two years in a population of postmenopausal women[39].

Sex differences in fluctuation of MMPs due to the cyclical tissue breakdown required for menstruation[40-42] should be given close consideration, as many chronic illnesses, including Long COVID and ME/CFS, disproportionately impact females. Progesterone downregulates MMPs and

can either trigger or prohibit the sloughing of the endometrium to support a pregnancy[40]. Anecdotally, Long COVID and/or ME/CFS patients who menstruate have reported significant symptom fluctuation throughout their menstrual cycles, in addition to bleeding pattern changes after a COVID-19 infection[43] and even COVID-19 vaccination[44-46]. Dysregulation of MMPs has also been implicated in uterine pathologies like endometriosis[40-42]. The impact of menstruation or illness on systemic collagenase activity and chronic symptoms is largely unexplored. Sex differences in MMPs raise the important question of whether the biologically conserved process of menstruation that is necessary for perpetuating the human species also comes at a cost associated with a higher risk for systemic barrier permeability or pathogen translocation. Namely, do the sex differences in MMPs required for the cyclical tissue breakdown of the endometrium put menstruating people at a higher risk for infection, disease, or cyclical symptom exacerbation?

How to test the hypothesis

Testing the main hypothesis in patients with Long COVID and/or ME/CFS would require a Phase 3 double-blind, placebo-controlled, randomized trial of participants in 4 potential treatment arms, including the two FDA approved low-dose options that could be considered for expanded use.

1) Doxycycline (Oracea®) 40 mg capsule per oral route once daily

2) Doxycycline hyclate (Periostat®) 20 mg tablet per oral route twice a day

3/4) Matching placebo of each

Investigators should assess for symptoms before and after treatment with validated questionnaires, physical assessment, and lab measurements of MMP-9 (Labcorp has a commercially available assay)[42], plus other objective metrics of common symptoms, such as the NASA lean test for autonomic dysfunction[43], the Beighton Score for hypermobility[44], CNS Vital Signs[45] or BrainCheck[46] for cognitive impairment, and abbreviated Depaul Symptom Questionnaires (DSQ-SF[47] or DSQ-PEM[48]) for post-exertional malaise. For a chronic illness with no existing cure, another important question is how long a patient can take these therapies safely. Therefore, treatment duration should be at least 6 months with potential for crossover design extending to 1 year. Additionally, by using data and frozen blood samples collected from existing funded and IRB approved research like the MIT MAESTRO Study, baseline levels of MMPs in a chronic illness population could be assessed in acute Lyme disease, Long Lyme, and Long COVID, compared to healthy controls. Participants could be followed to pair additional blood samples timed prior to or during menstruation. Menstruation is a complex and modifiable variable that can influence both chronic disease state and treatment response. However, this variable also suggests that hormone modulation or suppression of menstruation could potentially help some patients.

No FDA approved treatments for Long COVID or ME/CFS currently exist. Access to off-label therapies continues to be a significant barrier for patients who are suffering. Urgent funding must be prioritized to

study multi-pronged treatment regimens, including repurposed drugs with established safety profiles. LDD holds unique promise to aid in tissue repair by interfering with a pathologic immune response, while not causing immune suppression, which is a primary concern in patient populations with established latent infections and diseases caused by pathogens capable of persistence.

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Hypothesis

Could vascular damage caused by massive inflammatory events underlie a relapse/recovery phenotype of ME/CFS and Long COVID?

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Abstract

I hypothesize that there is a relapse/recovery type of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Long COVID in which a massive inflammatory event—like the inflammatory cascade prompted by the restoration of blood flow (reperfusion) to tissue that had been deprived of blood (ischemia) or an allergic or pseudoallergic reaction—causes substantial damage to blood vessels, launching a more severe phase of ME/CFS. People with Ehlers-Danlos syndrome and other connective tissue disorders may be at particular risk of this phenotype due to having connective tissue (a key component of blood vessels) that is more easily and severely injured during inflammatory events and slower to heal, causing a much longer recovery.

Hypothesis

My daughter has experienced two major "relapse events" in the five years of her myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) illness. The active phase of the first event, in October 2017, lasted only 15 minutes, but left her so weak she could barely walk. The active phase of the second event, in July 2020, lasted about two hours, and initiated a period of very severe disease.

Both events were biphasic, with an initial period of feeling very hot (and in one case red all over) followed, several hours later, by whole body shaking/chills and, during the second episode, electric-like zaps and wave-like cascades up her torso.

In my daughter's experience, these baseline-lowering events are distinct phenomena from day-to-day post-exertional malaise. Unlike the symptoms of post-exertional malaise, which are very impactful but

temporary, the relapse events led to major degradations in her condition that have persisted for many months. In the two and half years since the last relapse event, my daughter has made substantial progress toward recovery, but still has not yet regained her June 2020 level of functioning.

As I have worked to better understand my daughter's various interrelated chronic conditions—which include ME/CFS, hypermobile Ehlers-Danlos syndrome, craniocervical instability, Chiari malformation, tethered cord syndrome, and suspected mast cell activation syndrome—I have connected with many other individuals that have experienced a similar relapse/recovery pattern to their illness. Despite this lived experience, there is very little focus on this pattern in the existing research literature on ME/CFS and Long COVID. A notable exception is a recent preprint that documents epigenetic changes that occur following relapses in two patients with ME/CFS[1] and a subsequent paper that incorporates this analysis into a model of chronic neuroinflammation in ME/CFS[2].

Drawing on my daughter's experience and a review of the research literature, I hypothesize that there is a relapse/recovery phenotype of ME/CFS and Long COVID in which susceptible individuals experience massive "relapse events" that cause substantial vascular damage, launching a more severe phase of ME/CFS or Long COVID. Since many of the most prominent symptoms experienced by people with ME/CFS and ME/CFS-type presentations of Long COVID are systemic, the vascular injury is most likely caused by a systemic inflammatory process. I propose that the inflammatory events can be triggered through a range of different mechanisms, including thrombotic events that lead to ischemia/reperfusion injury, anaphylactic or anaphylactoid mast cell activations, or the inflammatory cascade of an acute infection.

Ischemia-reperfusion injury is one likely cause of systemic vascular injury given the heightened risk of thrombotic events after even mild cases of COVID-19[3] or other viruses[4] and the triggering of powerful and often injurious inflammatory processes during reperfusion, including "TLR-mediated pathways, chemoattractants, the complement cascade," and reactive oxygen species (ROS)[5]. Kell and Pretorius have written about the possibility that ischemia-reperfusion injury plays an important role in Long COVID and ME/CFS[6]. An alternative pathway for vascular injury is mast cell activation during an anaphylactic or anaphylactoid event in response to a pharmaceutical or chemical irritant, which similarly involves the complement system and other powerful inflammatory processes[7,8]. Vascular injury could also result from a cytokine storm prompted by an acute COVID-19 infection.

This hypothesis is consistent with a recent paper that found evidence of a unique signature of vascular transformation factors in people with Long COVID associated with the process of repairing damaged blood vessels[9]. It is also consistent with the findings of endothelial dysfunction in people with ME/CFS and Long COVID[10,11]. In a series of hypothesis papers[12,13], Wirth and Scheibenbogen (2021) and Wirth and Scheibenbogen (2022) explore how endothelial dysfunction, microvascular permeability,

and the resulting leakage of protein-rich fluid can give rise to many commonly reported ME/CFS symptoms. However, their proposed mechanism does not explain why some individuals experience major relapses followed by periods of slow recovery.

I propose that the vascular hyperpermeability (characterized by the excessive leakage of protein-rich fluid from blood vessels) that prompts many symptoms in ME/CFS—and likely, ME/CFS-type presentations of Long COVID—can arise from several additional mechanisms beyond the one noted by Wirth and Scheibenbogen, including through direct injury to the vascular endothelium[14]. A significant vascular injury, prompting the degradation of an individual's condition and the start of a more severe phase of illness, followed by the healing of that injury over time, could help explain the relapse/recovery pattern experienced by some individuals with ME/CFS and Long COVID.

A study in Sweden of 229 individuals with ME/CFS found that half had generalized joint hypermobility, a marker of connective tissue disorders like Ehlers-Danlos syndrome (EDS)[15]. Another study similarly found a much higher rate of hypermobility among people with ME/CFS and fibromyalgia than among comparison households[16]. People with EDS and other connective tissue disorders may be at particular risk of this relapse/recovery phenotype due to defective connective tissue that is more easily and severely injured during inflammatory events. As one researcher noted in a case study of recurrent venous thrombosis in an individual with hypermobile EDS, "In all types of EDS, the collagen that supports blood vessels is unusually weak and elastic, making blood vessels more prone to injury"[17,18]. People with EDS similarly experience poor and delayed wound healing[19], which may explain the long length of the recovery phase.

In people with a connective tissue disorder, the connective tissue degradation initiated by the inflammatory event can also cause or exacerbate craniocervical instability and other spinal problems, as well as vascular compression syndromes. These complications could potentially cause additional symptoms in affected individuals.

I would likewise expect that, even after healing, susceptible individuals remain at risk of future inflammatory events that could trigger another relapse.

Unanswered questions

Could some massive inflammatory events stem from vertebrobasilar ischemia or autonomic dysreflexia secondary to the spinal complications of severe hypermobility?

Is the lymphatic vasculature also injured in massive inflammatory events, exacerbating symptoms during the severe phase?

During the severe phase of a relapse/recovery phenotype of ME/CFS and Long COVID, do chronic inflammation and platelet activation slow recovery of the vasculature by preventing healing and/or exacerbating the injury?

How does the relapse/recovery cycle relate to microclots, autoantibodies, and other less cyclical disease components; are they alternative phenotypes, or do they coexist?

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Hypothesis

Astrocyte dysregulation of sympathetic nervous system causes metabolic dysfunction in subset of Long COVID and ME/CFS patients

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Abstract

An overactive sympathetic nervous system (SNS) may cause one subtype of Long COVID. People who are genetically at risk for noradrenergic nerve problems may develop an overactive SNS after an infection. Alternatively, genetic or virus-induced dysregulation of astrocytes could lead to overactivation of the SNS. An overactive SNS could disrupt regulation of immune cells, energy metabolism, sleep homeostasis, respiratory rate, gastrointestinal function, and systemic and cerebral blood pressure, causing fatigue and cognitive dysfunction.

Hypothesis

Long COVID refers to symptoms that continue for more than four weeks after onset of acute COVID-19 illness. This umbrella term includes a wide variety of symptoms and presentations. Long COVID patients may have different types of biological dysfunction, meaning that there may be distinct subtypes of Long COVID. One possible subtype is sympathetic nervous system (SNS) over-activation. This subtype may exist in both Long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)[1].

Underlying mechanisms of the SNS overactivation subtype

Theoretically, patients with this subtype already have a genetic dysregulation of neuronal norepinephrine (NE) release/clearance or noradrenergic receptor sensitivity[2]. This latent genetic dysfunction of NE signaling may not cause significant problems unless there is a trigger that causes excess NE release. As NE affects immune cell signaling, this could result in an over-activation or prolonged activation of the immune system in response to infection with SARS-CoV-2, the virus that causes COVID-19[3]. This

subtype could explain why ME/CFS is often triggered by a virus or brain injury, as these occurrences can trigger noradrenergic signaling[3].

Possible mechanisms for the SNS overactivation subtype include viral reservoirs, antibody reaction, and dysregulation of noradrenergic receptor expression. In Long COVID patients, viral antigens and reservoirs that remain in the body long after the initial infection may keep the overactive immune system in an inflammatory state[4,5]. A healthy person may not react to these SARS-CoV-2 reservoirs, as their functional immune cells should develop immune tolerance. Another possibility is that the immune system is reacting to SARS-CoV-2 antibodies.

Finally, it is possible that excess extracellular NE could keep the SNS and noradrenergic systems in the brain stuck in an overactive state. A prolonged period of increased levels of extracellular NE could lead to dysregulation of noradrenergic receptor expression. The excess extracellular NE may be due to a prolonged release of excess NE during the initial infection, or a failure of the negative feedback mechanisms that should reduce NE release.

Symptoms of an overactive SNS

An overactive SNS explains many of the symptoms found in Long COVID patients, such as IBS/gastrointestinal symptoms[6], heart palpitations[7], and sleep disturbance[8]. Additionally, in orthostatic intolerance, which is common in Long COVID and ME/CFS, the release of NE causes pronounced tachycardia. This rapid heart rate may cause palpitations, breathlessness, and chest pain[9].

Dysfunctional energy metabolism causes fatigue and cognitive dysfunction

An important piece of the puzzle is to explain how a dysregulated SNS could lead to chronic fatigue and brain fog (cognitive dysfunction). The most likely explanation is a dysregulation of metabolic function. There are many ways excess NE could affect metabolism, including enhancing aerobic glycolysis and depleting glycogen stores.

Excess NE or hypersensitive astrocyte β2 adrenergic receptors deplete glycogen stores

ME/CFS researchers have previously suggested that ME/CFS patients have dysfunctional neuroglia in the brain[10]. Astrocytes are a type of glial cell involved in brain metabolism and the regulation of glutamate and GABA. NE activation of β2 adrenergic receptors (β2ARs) on astrocytes results in increased expression of the glucose transporter GLUT1, leading to increased glucose uptake, enhanced aerobic glycolysis, and increased lactate production[11]. Increased lactate levels have been found in the brains of ME/CFS patients[12].

In the brain, glycogen is primarily stored in astrocytes, and glycogenolysis is activated by NE acting on β2ARs. Increased NE levels could therefore

lead to excessive glycogen depletion in astrocytes. It is also possible that the β2ARs themselves are oversensitive (not reducing their sensitivity in response to excess NE levels) due to genetic dysregulation[13].

β2AR autoantibodies have been found in a subset of ME/CFS patients, which could cause dysregulation of astrocytic metabolism via β2ARs[14]. High levels of CCL2/MCP1 have been found in ME/CFS patients and CCL2/MCP1 can increase β2AR expression[15,16].

An imbalance in astrocytes toward increased glycolysis could lead to reductions in glycogen stores in astrocytes. This could lower energy reserves, leading to increased fatigue. Researchers have proposed that brain glycogen decreases with increased periods of wakefulness, and that a major function of sleep is to replenish glycogen stores in the brain[17]. Therefore, an inability to build up glycogen stores in astrocytes could explain why many ME/CFS patients wake up feeling unrefreshed and tired[18].

Excess NE release could also contribute to the post-exertional malaise experienced by ME/CFS and Long COVID patients after exercise. If patients start with depleted glycogen stores, the increased NE release during exercise would further deplete glycogen stores.

Alternate subtype: Low norepinephrine/desensitized β2 adrenergic receptors

It is possible that in some ME/CFS and Long COVID patients, the biological mechanisms are the opposite to what has been suggested in this paper[19]. Reduced NE or reduced sensitivity of β2ARs could also contribute to fatigue, via a reduction of astrocytic glucose uptake, reduced glycogen synthesis, and a decrease in the lactate supply to neurons. This possibility aligns with research which has suggested that ME/CFS patients can be split into two groups with high and low NE plasma levels[20]. Reduced astrocytic glucose uptake could lead to a reliance on glutamine oxidation to maintain the tricarboxylic acid cycle. Desensitized β2ARs on immune cells could lead to an inability to switch from the production of pro-inflammatory cytokines such as tumor necrosis factor-α to anti-inflammatory cytokines. Research has shown that the capacity of monocyte β2ARs to regulate the production of tumor necrosis factor-α is reduced in ME/CFS patients[21].

β2 adrenergic receptor dysfunction throughout the body

Dysregulation of β2ARs could also cause excessive vasoconstriction of the blood vessels, bronchoconstriction of the lungs, reduced gut peristalsis, and dysregulation of lipolysis and thermogenesis in adipocytes. The β2AR also controls glycogenolysis and gluconeogenesis in the liver,

which could lead to depleted liver glycogen stores and a reliance on noncarbohydrate metabolites. In skeletal muscle β2ARs can control translocation of GLUT4, which is normally triggered during exercise in order to increase glucose uptake. A reduced ability to translocate GLUT4 could lead to skeletal muscle fatigue during exercise.

Astrocyte control of the sympathetic nervous system

A further theory is that dysfunction of the β2ARs on astrocytes could be *solely* responsible for causing the symptoms of ME/CFS and Long COVID. Astrocytes that reside alongside central nervous system sympathetic control circuits can regulate cerebral perfusion, systemic arterial blood pressure, heart rate, respiratory rhythm-generating circuits, sleep homeostasis, and glucose metabolism[22-24].

Of particular interest is that astrocytes detect falling cerebral perfusion pressure and activate sympathetic control circuits in response. To counter the dropped pressure, the sympathetic control circuits increase heart rate and systemic arterial blood pressure in order to maintain blood flow and oxygen delivery to the brain. This mechanism involves astrocytic calcium-dependent signaling pathways[25]. Dysregulation of astrocytic calcium signaling due to β2AR dysfunction could lead to an inadequate or excessive SNS response when an ME/CFS patient stands up. A dysregulated SNS response could explain the postural orthostatic tachycardia syndrome (POTS) symptoms of altered heart rate and dizziness experienced by many ME/CFS and Long COVID patients.

An initial overactivation of the SNS could dysregulate astrocytes via adrenergic receptors, which in turn could prevent the astrocytes from being able to effectively control the SNS. Alternatively, genetic or virus-induced dysfunction of astrocytes could be the root cause of SNS dysfunction, an idea given weight by the finding that SARS-CoV-2 is able to infect and replicate in human cortical astrocytes[26,27]. Research testing these hypotheses is needed in order to better determine the mechanisms of Long COVID and ME/CFS.

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Hypothesis

Increasing serum soluble CD40 ligand (sCD40L) may be a biomarker of ME/CFS and chronic Long COVID progression

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Abstract

To date, no single blood lab test exists to diagnose or track ME/CFS or chronic Long COVID. Based on existing literature, this article brings together evidence that a molecule secreted by the immune system called sCD40L tends to become increasingly elevated in ME/CFS, Long COVID, and Multiple Sclerosis. These studies, along with what's known about the role of sCD40L in health and other diseases, suggest sCD40L may be useful to track over time in ME/CFS and Long COVID patients.

Hypothesis

Many studies into myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Long COVID (LC) have sought to identify serum or plasma biomarkers. Most have focused on a single point in time, with a growing number identifying multi-marker "signatures" which can accurately classify patients versus healthy controls[1-3]. Some studies have investigated biomarkers at distinct time points with respect to condition, such as before and after exercise which is known to provoke ME symptoms[4,5].

Few if any LC and/or ME/CFS biomarker studies have been *longitudinal*, i.e., tracking the evolution of candidate biomarkers in individual patients over time.

One study from Hornig et al. (2015) explored candidate biomarker time-evolution at the group level, comparing plasma cytokine levels for ME/CFS patient cohorts that were early (< 3 years) and later (> 3 years) in their disease course[6]. They remarked on one cytokine in particular: soluble CD40 ligand (sCD40L) between the early and late stage ME/CFS

patient cohorts, which showed a highly significant progression ($p<0.00001$ via null hypothesis testing).

ME/CFS is often a post-viral illness[7], and recently further evidence has emerged for the progression of sCD40L levels in other post-viral illnesses:

- Wu et al. (2021) reported on sCD40L as a marker of *progression* in multiple sclerosis (MS), with a clear increase between cohorts in the earlier (relapsing-remitting) and later (secondary progressive) forms of the disease[8]. Recent evidence indicates MS also has a viral trigger, specifically Epstein-Barr virus[9].
- Patterson et al. studied sCD40L levels in chronic Long COVID cohorts (with predominantly ME/CFS-like symptoms), reporting significant but modest sCD40L elevation in an early study[10] and a stronger significant correspondence of sCD40L levels to LC severity (across 4 of 5 symptom questionnaires) in a later study[11].

These studies each point to increasing sCD40L correspondence with progression (time and/or symptom), giving rise to the hypothesis that **sCD40L levels progressively increase on average during the course of chronic Long COVID and ME/CFS**. Whereas Hornig et al. (2015) and Patterson et al. (2021) found opposing effects at an early timepoint for ME/CFS and LC, respectively, both showed evidence for a progressive increase in sCD40L levels. Such progression on average may give indications about the disease mechanism(s), while such progression individually may be an indicator of disease presence and/or severity.

Soluble CD40 ligand (sCD40L), alternatively known as CD154, is a mediator of CD40 receptor immune and inflammatory responses ubiquitous across immune cell types. The ligand form was originally found on the surface of activated T-cells[12]. But more recently it is recognized platelets are likely the largest source of soluble (circulating) CD40L; and that sCD40L may in turn be the most ubiquitous signaling molecule in the platelet repertoire[13,14].

The platelet origin of sCD40L may comport with multiple findings of abnormal platelet activation for LC and/or ME/CFS using various experimental methods:

- Microscopic investigation of platelet-poor plasma from a cohort (n=80) of LC patients identified platelet hyperactivation as a candidate sign[15], with similar findings in a report of a smaller cohort (n=25) of ME/CFS patients[16].
- Flow cytometry study of LC patients (n=24) with confirmed cardiopulmonary exercise test (CPET) findings found two markers of platelet activation—P-selectin and platelet-leukocyte aggregates (PLA)—persistently elevated at 6 months post-infection[17].
- RNAseq study of ME/CFS patients (n=30) found abnormally enriched gene sets for platelets (but not other immune cells) post-exercise[18].

Beyond platelet activity dysfunction, several suspected pathological pathways for LC and ME/CFS have been linked to sCD40L signaling, including

endothelial cell activation[19], metabolism-associated cell danger signaling via monocytes[20], pathogen-associated molecular pattern (PAMP) activation of B-cell adaptive immunity[21], and neurocognitive impairment[22].
Taken all together, sCD40L levels in LC and ME/CFS appear to be a readily achievable (via blood sample) and potentially fruitful longitudinal measurement, which may serve as a progressive biomarker and/or an indicator of underlying pathological mechanisms.

Given its progression appears in MS, one caveat is in order: sCD40L is not apt to be a specific marker for LC and/or ME/CFS. It has also been implicated as a marker of cardiovascular disease including stroke[23,24] and for several other neurological disorders including Alzheimer's disease[25,26]. Any studies of this marker for LC and/or ME/CFS should be designed and interpreted accordingly.

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Community polls

Informal social media polls: SARS-CoV-2 reinfection and Long COVID, and the presence of new eye floaters in Long COVID and ME/CFS

Patient-Led Research Collaborative

Abstract

Generating and sharing polls on social media is one way that patient communities can informally test their theories and give researchers ideas about what to further explore. In February 2023, the Patient-Led Research Collaborative conducted two sets of informal polls on Twitter and Mastodon. One question was about Long COVID and reinfections, and the other asked about new eye floaters (myodesopsias) in patients with Long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). This brief article describes the results of each poll: 10.2% of Twitter respondents and 20% of Mastodon respondents reported experiencing Long COVID after a reinfection, rather than a first infection, and more than half of Twitter respondents with Long COVID or ME/CFS answered "Yes'' or "Maybe" that they noticed new eye floaters as a symptom. Both polls had limitations: Neither was intended to establish incidence or prevalence data, and the poll respondents are likely not representative of the overall Long COVID and ME/CFS communities. Despite this, the results provide potentially useful information for Long COVID and ME/CFS research and policy.

Introduction

Social media has been widely used for health purposes in the last decade, especially during the ongoing COVID pandemic[1]. Many platforms are important for patients and clinicians alike. A key way that patients source information about their illnesses or test their hypotheses among the patient community is by creating and sharing polls on social media. These polls come with limitations, however. For example, Twitter polls are unlikely to reach a broad sample audience, and the generalization of their results is limited[2]. Additionally, polls on Twitter are limited to four response options, and until very recently, posts could only be a maximum of 280 characters. Polls on Mastodon face similar constraints: For example, they also have only four response options. Despite the limitations to the conclusions one can draw from these polls, they

reveal insights that can help patients and researchers pursue hypotheses through more formalized research avenues. In February 2023, the Patient-Led Research Collaborative conducted two sets of informal polls on Twitter and Mastodon. Both sets of polls were anonymous: Twitter and Mastodon do not reveal who participates in their polls. We conducted these polls to test questions of importance to the Long COVID patient community and/or to build off hypotheses published as part of the first issue of the Patient-Generated Hypotheses Journal.

Long COVID after reinfections

The first set of polls was a question of importance to the Long COVID patient community. We asked whether an initial COVID-19 infection or a reinfection caused the onset of Long COVID symptoms (see Figure 1). There is limited data on reinfections and Long COVID. Bowe et al. (2022) and Hadley et al. (2023) reviewed electronic health records (EHRs) of patients and established that reinfections can cause an onset of Long COVID symptoms[3,4]. Bowe et al. (2022) found that "the risks of adverse health outcomes increased as the number of infections increased" in the acute and subacute phase (p. 2399). However, in the study, patients were only followed for six months after infection. Additionally, Bowe et al. (2022) included only patients with a positive SARS-CoV-2 test. Patients who may have been infected, but either were not tested or whose test showed a false negative, were not included in the analysis. This may have caused an underestimation of reinfection risks.

A systematic review published by Pecoraro et al. (2021) calculated that up to 58% of COVID patients may initially have a false negative polymerase chain reaction (PCR) SARS-CoV-2 test[5]. This means that there are limitations to the conclusions that can be drawn from studies which review EHRs for positive tests. Overall, there is limited information about the number of times people have been infected with SARS-CoV-2 and the risks associated with those reinfections. This informal poll collected additional data on the topic.

We asked users on Twitter and Mastodon the following question with results provided in-line and in *Figure 1*:

Twitter poll

At which infection did you first experience Long COVID symptoms? (n=664)

- ☐ 1st infection: 89.9%
- ☐ 2nd infection: 7.7%
- ☐ 3rd infection: 1.1%
- ☐ 4th infection or higher: 1.4%

Note: The results may not total to 100% due to rounding.

Mastodon poll

At which infection did you first experience Long COVID symptoms? (n=607)

- ☐ 1st infection: 80.0%
- ☐ 2nd infection: 14.0%
- ☐ 3rd infection: 3.0%
- ☐ 4th infection or higher: 3.0%

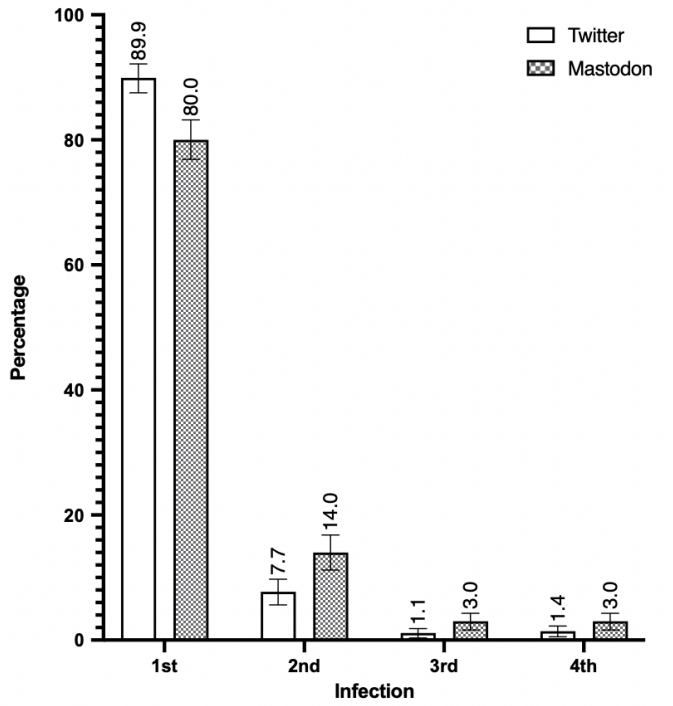

Figure 1. *Percentage of Respondents with Long COVID Who Developed Long COVID after a 1st, 2nd, 3rd, or 4th Infection or Higher*

We assumed that users who responded to these polls self-identify as having Long COVID. 89.9% of respondents on Twitter and 80.0% of respondents on Mastodon reported experiencing Long COVID after their first infection. 10.2% of Twitter respondents and 20% of Mastodon respondents reported experiencing Long COVID after a reinfection. Sample sizes between the platforms were similar with n=664 on Twitter and n=607 on Mastodon.

Note that this data does *not* indicate the likelihood of developing Long COVID after each infection. Rather, the data demonstrates after which infection a small sample of people in an online community developed Long COVID. There are important limitations to this data: for example, the poll did not allow respondents to indicate if they developed Long COVID after a first infection, then recovered, then developed it again after a subsequent infection. It is possible that those active in Long COVID social media communities have been sick for many months and are more likely to have developed Long COVID from their first infection. The poll also assumes that everyone who responded has Long COVID, with inclusion criteria not verified. Additionally, many people may not realize that they have Long COVID and therefore would be unable to respond to such a poll on social media.

Overall, however, the results suggest that Long COVID from reinfections does occur, and all people are at some risk of Long COVID, even if their prior infection(s) did not cause it. Bowe et al. (2022) and Hadley et al. (2023) support this conclusion[3,4]. Bowe et al. (2022) found that negative health outcomes "increased in a graded fashion according to the number of infections" (p. 2399). This has implications for both COVID mitigation policy and

research. Transmissibility of SARS-CoV-2 increases frequently from viral mutations, and many people have been infected multiple times. Therefore, it is more important than ever to mitigate transmission and research the effects of multiple infections on mortality and long-term health outcomes, including Long COVID.

Eye floaters

The second set of polls we conducted was in response to Matt Mazewski's hypothesis, which is included in this publication. The polls ask about the presence of *new* eye floaters (myodesopsias) in patients with Long COVID and ME/CFS. Because the poll refers to this condition by the name "eye floaters," for consistency, this article will continue to use that language. As Mazewski hypothesizes, in both Long COVID and ME/CFS, inflammatory triggers may cause collagen degradation that leads to the presence of eye floaters[6].

We asked users on Twitter and Mastodon the following questions with results provided in-line. Twitter results are also shown in Figure 2:

Twitter poll

If you have Long COVID, did you notice new eye floaters (spots in your vision that may look to you like black or gray specks, strings, or cobwebs) as one of its symptoms? (n=544 subtracting "see results")

- ☐ Yes: 37.1%
- ☐ No: 49.5%
- ☐ Maybe: 13.5%

Note: The results may not total to 100% due to rounding.

If you have ME/CFS, did you notice new eye floaters (spots in your vision that may look to you like black or gray specks, strings, or cobwebs) as one of its symptoms? (n=281, subtracting "see results")

- ☐ Yes: 38.5%
- ☐ No: 45.2%
- ☐ Maybe: 16.3%

Mastodon poll

If you have Long COVID and/or ME/CFS, did you notice new eye floaters (spots in your vision that may look to you like black or gray specks, strings, or cobwebs) as one of your symptoms? (n=76, subtracting "see results")

- ☐ Yes: 42.9%
- ☐ No: 44.4%
- ☐ Maybe: 12.7%

Note: Mastodon results not shown in Figure 2 due to small sample size.

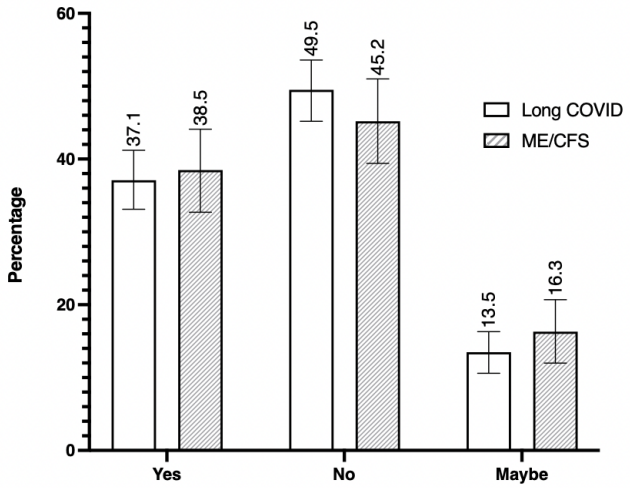

Figure 2. *Existence of New Eye Floaters among Twitter respondents with Long COVID and ME/CFS*

More than half of Twitter respondents with Long COVID or ME/CFS answered "Yes" or "Maybe" that they noticed new eye floaters as a symptom on the Twitter polls.

On Mastodon, where there is limited functionality when posting a thread with multiple polls, ME/CFS and Long COVID were grouped together in order to minimize confusion and obtain a larger sample size. Despite this, the sample size (n=76) was too small to include in our graph or analysis. On Twitter, the sample size was larger for the Long COVID question than the ME/CFS question: n=544 (Long COVID) and n=281(ME/CFS).

There are limitations to this informal poll. Given that a relatively small number of people on social media responded, it is not a representative sample of the larger Long COVID or ME/CFS populations. It is also not intended to provide incidence or prevalence data. Further, those who experienced eye floaters may have been more likely to answer the question, which may have skewed the data. The poll also assumes that everyone who responded has Long COVID or ME/CFS, but inclusion criteria were not verified. Despite these limitations, the response still indicates that many in the Long COVID and ME/CFS population do experience new eye floaters, and this could be an important topic for future research that is currently overlooked. As Mazewski discusses in his hypothesis, it is also possible that having eye floaters is a risk factor for Long COVID and ME/CFS.

Conclusion

Informal social media polls, while limited in many ways, are important for exploring health-related phenomena that patient groups may notice more readily than the general public. Creating these polls and disseminating results may allow patients and researchers to pursue areas of particular importance sooner than they otherwise would have. This benefits both patients and the larger medical community.

The role of reinfections in Long COVID is of great importance to the Long COVID community as well as to the public at large. The poll results suggest that while most people who are active in the Long COVID communities on Twitter and Mastodon experienced Long COVID symptoms at their first infection, reinfections did cause an onset of Long COVID symptoms for a significant number of people (10.2-20%). Bowe et al. (2022) established that multiple infections with SARS-CoV-2 increase the

risk for adverse health outcomes, including Long COVID[3]. There is a need for widespread public health warnings about the risks of COVID reinfection, not only in regard to mortality, but also to Long COVID.

In our second set of polls, more than half of poll respondents with Long COVID or ME/CFS answered "Yes" or "Maybe" that they experienced new eye floaters as a symptom, indicating that this is perhaps an avenue worthy of future research, despite the limitations of polls discussed previously. The topic serves as one example of an area of study where patients are, perhaps, more aware of a health phenomenon than many scientists or researchers may be. Continuing to develop hypotheses, testing them informally via social media polls, and then disseminating the results to a larger audience is important for all patient communities, but especially for the patient communities of Long COVID and ME/CFS. These conditions are chronically underfunded and still not well-known among the medical community, despite the fact that Long COVID and ME/CFS affect tens of millions of people. Informal social media polls and wider dissemination of their results may be one way to move the needle toward more public awareness, research, and funding for Long COVID and ME/CFS.

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For more information on the panelists, please visit:
patientledresearch.com/projects/patient-generated-research-hypotheses

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Contact us

If you have any input on this issue, suggestions for future issues, or questions, please email our team at hypotheses@patientledresearch.com.