Post-COVID-19 syndrome: persistent neuroimaging changes and symptoms 9 months after initial infection

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SUMMARY

A previously healthy and active middle-aged woman acquired COVID-19 as an occupational exposure with subsequent persistent post-COVID-19 symptoms including headache, dyspnoea on exertion, chest pressure, tachycardia, anosmia, parosmia, persistent myalgia, vertigo, cognitive decline and fatigue. She presented to a tertiary medical centre for further evaluation after 9 months of persistent symptoms and had a largely unremarkable workup with the exception of a persistently elevated monocyte chemoattractant protein 1, blunted cardiovagal response and non-specific scattered areas of low-level hypometabolism at the bilateral frontal, left precuneus, occipital and parietal regions on PET scan.

BACKGROUND

A significant proportion of patients (estimated at greater than 10%) developed persistent symptoms after recovering from initial infection COVID-19.[1–6] This persistent symptomatology is referred to by the National Institutes of Health (NIH) as postacute sequelae of COVID-19 infection (PASC) and by various names including 'long COVID-19', 'long haulers' and 'post-COVID-19 syndrome' by other groups. The symptomatology of post-COVID-19 syndrome bears significant resemblance to several other postinfectious syndromes such as those that follow Lyme disease, Epstein-Barr Virus (EBV), cytomegalovirus (CMV) and Zika infection, as well as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), fibromyalgia and postural orthostatic tachycardia syndrome (POTS).[7–19] Currently, not much is known about the pathophysiology of post-COVID-19 syndrome, but previous data from other related syndromes suggest immune dysregulation as a central cause that can lead to alteration in brain activity as measured on functional imaging.[20–22] To our knowledge, this is the first comprehensive case report of detailed findings including abnormal PET brain imaging in the evaluation of a patient with post-COVID-19 syndrome at this time point.

CASE PRESENTATION

A middle-aged woman with a medical history significant only for hypothyroidism presented to a tertiary medical centre for evaluation of a 9-month history of persistent headache, dyspnoea on exertion, chest pressure, tachycardia, anosmia, parosmia, myalgia, vertigo and fatigue that started after an occupational infection with COVID-19. Shortly following her exposure to COVID-19, which occurred during an occupational exposure in December 2020, she had initial symptoms of fever, dyspnoea, cough, anosmia, fatigue and dysgeusia, as well as rhinorrhoea and left eye pain similar to sinusitis. She was not admitted at this time but was prescribed a 3-week course of dexamethasone. Since that time, her anosmia had continued with the addition of parosmias of burning or foul odour. She continued to experience significant fatigue that ultimately decreased her exercise tolerance and was accompanied by brain fog, chest pressure, dyspnoea on exertion and tachycardia with minimal activity. She noted a decline in cognitive function including short-term memory deficits and an inability to multitask. In January 2021, she awoke with severe dizziness characterised by debilitating vibration sensations and imbalance. She thereafter developed both persistent vestibular dysfunction as well as a persistent headache, which was focused behind her left eye and her left parietal area accompanied by photophobia and phonophobia. She also developed significant pain issues including myalgias in her lower extremities, neck, back and anterior chest wall along with paresthesias in her face, especially on her left side. Additional symptoms through her course included but were not limited to diffuse skin changes, lower extremity oedema, emotional lability/irritability, partial focal seizures, insomnia, palpitations, tinnitus, speech difficulties and salivary gland pain with eating.

Vital signs were normal with a blood pressure of 112/75, oxygen saturation of 98% and pulse of 65, and physical examination was non-contributory except for multiple tender points in the abdomen, anterior chest wall, shoulders and neck.

INVESTIGATIONS

Her initial evaluation prior to being seen by our team included laboratory workup that included an elevated erythrocyte sedimentation rate (ESR) to 121 mm/hour, positive D-dimer of 1.41 ng/mL

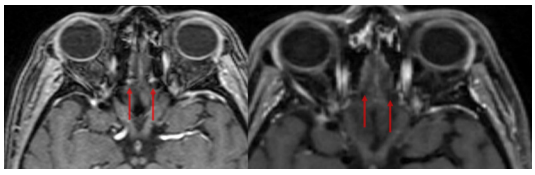

Figure 1 Mild olfactory enhancement noted on initial MRI, resolved on follow-up.

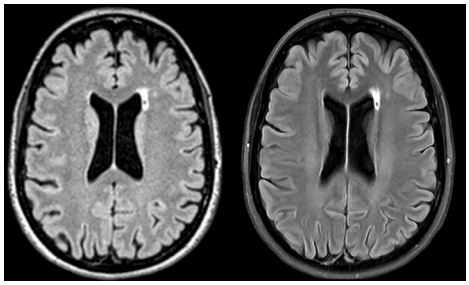

Figure 2 Non-enhancing T2 signal white matter changes at the anterior left frontal lobe especially along frontal horn lateral ventricle, as well as a non-specific tiny focus of superior left frontal lobe, unchanged between MRIs.

(upper limit of normal 0.50) and neutrophilic predominance of 86% on complete blood count (CBC) differential. A brain MRI demonstrated non-specific white matter changes and minimal olfactory enhancement in January 2021, and a fluoroscopic guided lumbar puncture in March 2021 that was negative for infectious causes of her headaches. Two identical gamma restriction bands were observed in serum and cerebrospinal fluid (CSF) indicative of systemic rather than intracerebral synthesis of gammaglobulins. Videonystagmography testing was abnormal as evidenced by left unilateral weakness and biphasic nystagmus. She additionally had an echocardiogram in July 2021, which was technically limited but reported mild-to-moderate aortic insufficiency and mild aortic sclerosis. A 7-day cardiac monitor performed at the time was negative for worrisome arrhythmias.

Echocardiogram repeated at our institution demonstrated ejection fraction of 71% and normal valves with normal ventricular function with no wall motion abnormality. MRI of the brain repeated 8 months later redemonstrated non-enhancing T2 signal changes in the white matter of the anterior left frontal lobe especially along the frontal horn of the lateral ventricle but otherwise unremarkable (figures 1–3). PET CT of the brain using ^{18}fluorodeoxyglucose for metabolic evaluation revealed non-specific scattered areas of low-level hypometabolism at bilateral frontal, left precuneus, occipital and parietal regions (figures 4 and 5). Quantitative axonal sweat reflexes were normal, heart rate was augmented by 12 on tilt-table testing without significant decrease in blood pressure, and heart rate responses to deep breathing were reduced on autonomic reflex screening.

Laboratory testing here showed a normal complete blood count and complete metabolic panel. Inflammatory markers were no longer elevated given an ESR of 2 mm/hour and a CRP of <3.0 mg/L. D-dimer was also within normal limits. Endocrine testing including dehydroepiandrosterone, free thyroxine and triiodothyronine levels were all normal, though

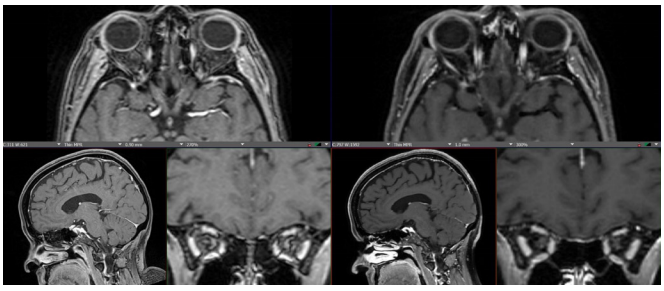

Figure 3 Prominent perivascular spaces in the right greater than left basal ganglia were visualised on MRI.

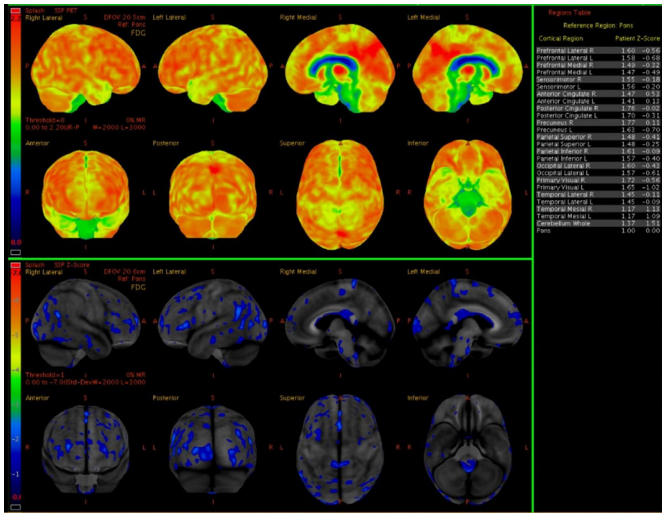

Figure 4 Global view of PET scan results performed at 9-month mark. The majority of Z-scores are noted to be in the negative range consistent with widespread hypometabolism.

thyroid-stimulating hormone was low at 0.03 mIU/L (lower limit of normal 0.3 mIU/L). Thyroperoxidase antibody was negative at 1.2 IU/mL. An extended autoimmune workup with ANA, CCP, double-stranded DNA, SSA, SSB, Smith, RNP, Scl 70, Jo 1 and rheumatoid factor was negative. Serum protein electrophoresis was negative. Cytokine panel testing showed normal levels of tumor necrosis factor (TNF), Interleukin(IL)-6, interferon beta, IL-10, IL-1 beta, interferon gamma, macrophage inflammatory protein (MIP)-1 alpha, Granulocyte Macrophage Colony Stimulating Factor (GM-CSF), IL-2 receptor alpha soluble, interferon alpha and IL-18 with an elevated level of monocyte chemoattractant protein (MCP)-1 at 228 pg/mL (upper limit of normal 198 pg/mL).

DIFFERENTIAL DIAGNOSIS

This patient had a constellation of symptoms that most closely resemble post-COVID-19 syndrome, with features similar to that seen in both ME/CFS and fibromyalgia. It was important to evaluate for potential alternative diagnoses including autoimmune diseases, endocrine disorders and other inflammatory disorders. She had an extensive largely negative workup that is consistent with that expected of the post-COVID-19 syndrome. Importantly, she did show a few markers that could potentially be helpful in the diagnosis of post-COVID-19 syndrome including an elevated MCP-1, blunted vagal response and hypometabolism on brain PET scan.

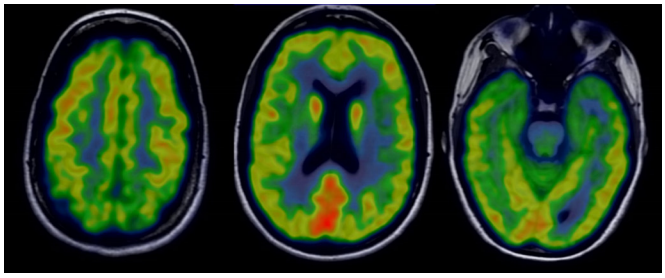

Figure 5 Transverse view of PET. Non-specific scattered areas of low-level hypometabolism are present at the bilateral frontal, left precuneus, occipital and parietal regions. Notably, the gyrus rectus is spared.

Patient's perspective

Backstory: before testing positive for COVID-19 in December 2020, I was a fully employed, healthy woman. I have always been exemplary in my diet, supplement, and exercise regimens – and often got razzed about it! My husband and I live on a farm in a rural area. We have horses and love to trail ride. We have ATVs and a lovely in-ground pool. We also have cattle and goats, and have been active with our family in 4-H. We have always had a garden and beautiful flower beds. I was heavily involved in the loving maintenance required to sustain all of these things—I absolutely love country life.

While at my job, I had several occupational exposures to COVID-19 without a fit-tested N95 mask for PPE.

Within 36 hoursof exposure, I developed a fever of 102 and felt miserable. I tested positive the next morning for COVID-19. My symptoms included lots of upper respiratory drainage with sneezing, headaches, cough, fever, body aches, diarrhea, SOB with exertion, heart palpitations, and extreme fatigue. The Occupational Medicine NP prescribed a Z-Pak and dexamethasone three week taper dose. I expected two weeks off and full recovery, as I have always been very healthy - why wouldn't I snap back? However, I have been unable to work since.

My initial COVID-19 infection was resolving, but I was still extremely fatigued. Exactly two weeks after testing positive for COVID-19, I began to have strange new symptoms—without any similar history prior to COVID-19. I was dizzy, my head had vibration-like pressure, brain fog, tinnitus, sore joints and muscles, GI upset—I was still so exhausted. I was prescribed Bactrim by my Occupational Medicine NP, guessing it was an inner ear infection—two additional weeks expected for recovery.

I then elected to see my trusted ENT as these new symptoms persisted. Testing was done, I was diagnosed with the COVID-19 virus affecting my vestibular system, tinnitus, and mild-to-moderate unilateral hearing loss. I was given vestibular exercises to do at home, was told 8–12 weeks to recovery if I pushed through the exercises and desensitized my vestibular system. I was given vertigo restrictions by ENT—no driving, swimming, or operating heavy equipment. The vertigo restrictions are still in place nine months later.

Then, days later, came a migraine-like headache behind my left eye and across my left temple and scalp. That evening, I experienced an episode while in bed which started with a feeling of euphoria, followed by twitching in the left arm which migrated to the left side of my face with facial spasms around my left eye and down to my cheek, with residual numbness into the left arm and face which lasted for hours. My left temple has remained so tender that I am unable to sleep on my left side.

The migraine continued, then worsened behind my left eye and left temple, causing me to visit the ER to rule out stroke in January 2021. CT was negative; however, MRI showed some irregularities. Depression set in with a feeling of impending doom, especially at night. Very emotional. Migraines have persisted since January.

Foggy thinking worsened with short-term memory problems, inability to multitask, confusion, difficulty verbalizing appropriately—which led to irritability, more anxiety and depression. My personality is 'flat', nothing like my former self. I am still plagued by all of these symptoms.

Neurologist consulted: vertigo, anxiety, hemifacial spasms, and migraine following COVID-19 were diagnosed. Rest and

Continued

Patient's perspective Continued

vestibular physical therapy ordered—six months postinfection, full recovery anticipated. Psychologist recommended for anxiety and depression. Weekly psychotherapy by phone starting in early April—very stabilizing but exhausting.

In March, rash broke out on the forehead, cheeks, and nose with sun exposure, again no history of skin problems. Dermatologist seen; told COVID-19 causes rashes, given topical rosacea medication—no results. Rash extended into scalp with hair loss. Topical steroid prescribed, relieved scalp symptoms. Heavy sunscreen and hat required while outside, rash still present.

ENT ordered VNG vestibular testing for my continuing in balance symptoms. Concerning nystagmus found along with other problems. Testing was so tiring and sensitizing, five days complete rest were required afterwards. My brain felt like I had a TBI. ENT corresponded with PCP with grave concerns when testing results were received showing 'central' damage.

Heat and cold intolerance developed; heat caused dizziness and profuse sweating, cold causing Raynaud's in fingers and livedo reticularis on extremities and abdomen.

Neuropathy developed, first in my toes, then fingers—like a bee sting, lasting several minutes to a few hours, onset in the evening. Left facial and scalp numbness has also persisted.

Physical therapist evaluation spawned new recommendation to Neurologist for vision OT and speech therapy. My symptoms were worsening: balance, vision, and speech were all involved. PT worked on inner ear crystals using the canalith repositioning procedure for weeks, imbalance unimproved.

Severe insomnia—everything hurt. Melatonin started by Neurologist recommendation. Complete exhaustion.

Neurologist reassessment with new orders for lumbar puncture and blood testing for multiple disorders, including MS, results largely negative. Orders to continue PT, added vision OT and speech therapy. Trazodone started for insomnia. With worsening symptoms at next neurologist appointment, amitriptyline was started briefly with intolerable side effects, and trazodone was resumed.

Eyes checked by three specialists due to persistent pain behind left eye, difficulty focusing, photophobia, shapes appearing in my visual field. All three specialists concluded there was nothing wrong with my eyes—'it's not your eyes causing the problem…'

Weekly PT, plus new vision OT and ST were started. This routine kept me completely exhausted—like I was on a roller coaster. I slept for days after each therapy session, then repeat.

During a PT evaluation of my nystagmus utilizing a head roll maneuver, I had another 'episode' which started with a feeling of euphoria/fear, bursting into tears uncontrollably, and my left leg and arm had twitching that 'marched' up into my face, around my left eye, down into my cheek, then around the left side of my mouth. This episode was stronger and made me realize that the 'episodes' I was experiencing were actually Focal Aware Seizures.

Every body system was negatively affected by June. Then I developed weight gain with generalized edema, and 2+ pitting edema in my left ankle and foot, chest discomfort, frequent heart palpitations, bradycardia, and greater SOB with exertion. My PCP ran testing for 'everything [she] could think of'. TSH low normal, thyroid medication dose was increased. A proBNP was elevated to 253 - Entresto started for what appeared to be mild heart failure. Echo showed mild-to-moderate aortic insufficiency. Heart monitor showed bradycardia to 37bpm to tachycardia in

Continued

Patient's perspective Continued

the 130s with arrhythmias at rest. PCP discussed my worsening symptoms and my husband asked if she would refer me to a tertiary care center so we could get some answers—she agreed and contacted the referral center immediately. Neurologist consulted and agreed with PCP, stating this center would be their next recommendation.

My husband and I had been raised to believe this particular referral center is the place to go when you really need medical help. We were completely exhausted, confused, and angry after evaluations and testing by a myriad of local doctors, specialists, and therapists—all with largely negative testing results and similar or conflicting phrases. 'COVID-19 is new, there aren't any scientific studies yet' and 'these symptoms may be COVID-19 related, we just don't know about COVID-19'. Or, the 'you should be recovered after ___ weeks/months' teamed with 'you need to completely rest', or 'you need to desensitize your vestibular system and stay active to get better'.

I was over six months post COVID-19 infection walking with a Rollater and still unable to drive a car. I had intolerable, worsening symptoms and no answers—my husband and I were both physically and emotionally drained. When the referral center called me, wanting to schedule an appointment - I literally cried! It was three months wait to be seen at their Post COVID-19 Clinic, but they gave me that the hope I desperately needed. All of my local doctors and therapists were eager to get their answers too!

We drove over 600 miles to the Post COVID-19 Clinic. It was definitely worth the drive. The facility was huge and intimidating at first, but everyone we spoke to was extremely helpful and courteous.

I cannot say enough good about my Post COVID-19 physician and his delivery of knowledge on Post COVID-19 Syndrome. For the first time, I was speaking with a doctor who understood what I had been going through and had answers! He thoroughly listened, answered questions and explained what he believed was causing my symptoms and the tests he was ordering to confirm. He and his staff were also very responsive, accommodating our need to see other specialists and having testing completed within as few days as possible. After my testing results were completed, he took the time to thoroughly explain what was found and my final diagnosis, answering all of our questions and laying out the Post COVID-19 Clinic plan of care for patients with Post COVID-19 Syndrome. For the first time since my symptoms began, I had hope!

As with my post COVID-19 physician, the three other specialists I saw, the nurses, and the technicians were all very professional and took time to do their job well and unhurried with excellent communication. Each employee seemed genuinely happy and engaged in their duties, all of which helped me to better tolerate a multitude of tests and appointments.

The patient education delivery was unique, given via Zoom meeting from home. Their Post COVID-19 Syndrome educational Zoom meetings were well-presented, engaging, and enlightening. For the first time, I fully understand why I feel like I do. More importantly, I now have guidance on how I can relieve symptoms by rethinking and differently managing my personal health practices. I will also be given a health coach for six sessions over the next six months to help me institute my new Post COVID-19 Syndrome plan of care.

Continued

Patient's perspective Continued

I cannot discuss what COVID-19 has done to me without mentioning what it has done to my husband. He has been there every step of the way and it has wreaked havoc on his mental and physical health. Without his dedicated support, I am unable to function independently. I cannot imagine being less fortunate and not having a support system with Post COVID-19 Syndrome.

DISCUSSION

PASC is remarkably heterogeneous in its presentation and may be better phenotyped by grouping patients by symptom clusters in order to better target treatment by applying lessons learnt from treating similar medical conditions. A subset of patients with PASC will present with a syndromic constellation of symptoms similar to that seen in other post viral illnesses, ME/CFS, fibromyalgia and POTS.[1–5 7] These patients are referred to by several terms including 'long-haulers' and 'long COVID-19' but are perhaps more appropriately described as having post-COVID-19 syndrome. Diagnosis of the post-COVID-19 syndrome is often frustrating for both patients and medical providers as while diagnostic criteria have been proposed, they have not been widely implemented.[23] Furthermore, these criteria are clinical, and there is no accepted diagnostic testing modality for post-COVID-19 syndrome at this time.

Here we present the case of a middle-aged woman with an occupationally acquired COVID-19 exposure that led to persistent post-COVID-19 symptoms and diagnosis of post-COVID-19 syndrome at 9 months. Salient features of this case include the presence of multiple phenotypes of post-COVID-19 syndrome including fatigue-predominant as well as myalgia-predominant features. We also demonstrate the myriad of symptoms that can be associated with persistent post-COVID-19 symptoms including but not limited to headache, dyspnoea on exertion, tachycardia, myalgia, anosmia/parosmia, vertigo, cognitive dysfunction, emotional lability and fatigue. At this time, existing data suggest that patients with persistent symptomatology, including those with fibromyalgia, ME/CFS and POTS, have a dysregulated immune response that may be responsible for the characteristic syndromic presentations. It is highly likely that this pathophysiology also occurs in patients with post-COVID-19 syndrome; indeed, preliminary data from our first 108 patients with post-COVID-19 syndrome does demonstrate an increased incidence of elevation of IL-6.[24] More recently, data have emerged demonstrating decreases in CD8+ T cells in patients with PASC compared with healthy controls and patients who had COVID-19 but did not develop PASC.[25 26] Patients with PASC have

Learning points

- The post-COVID-19 syndrome is common, occurring in approximately 10%–30% of patients who have recovered from acute COVID-19 infection.
- Patients with post-COVID-19 syndrome often have a constellation of symptoms that are life limiting but have a generally negative workup.
- Diagnosis of post-COVID-19 syndrome requires a high index of clinical suspicion.
- There are no definitive diagnostic tests for post-COVID-19 syndrome; however, we present the hypometabolic PET scan of the brain, elevated MCP-1 and blunted vagal response as potential supporting tests for the diagnosis of this prevalent condition.

also demonstrated a significant decrease in T regulatory cells and elevation in the CD14+, CD16+ and CCR5+ monocyte subsets.[26] Chemokine analysis in patients with PASC was also abnormal with significant elevations in CCL5/RANTES, IL-2, IL-4, CCL3, IL-6, IL-10, interferon gamma and vascular endothelial growth factor (VEGF) and significantly lower levels of GM-CSF and CCL4 when compared with healthy controls.[26] In light of these findings, the elevated MCP-1 observed in our patient may represent one feature of the immune dysregulation seen in PASC.

Studies have demonstrated hypometabolic changes on PET scan as well as altered brain recruitment in response to standard stimuli on functional imaging.[20–22] Similarly, patients in the early stages of post-COVID-19 syndrome (3–4 weeks after infection) have been demonstrated to have hypometabolic brain PET scans.[27–29] Review of our patient's PET scan demonstrates similarities to those presented by Guedj *et al*[27] but also shows sparing of the gyrus rectus. The significance of this imaging finding will be better demonstrated with larger study cohorts and may indicate a feature of the beginnings of recovery. Demonstrating that these changes are present at 9 months after infection supports the persistence of symptoms and implies that hypometabolic changes on brain PET scan may be a marker of continued post-COVID-19 syndrome and may be useful as a biomarker going forward.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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