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LETTER TO THE EDITOR

SARS-CoV-2 and *Toxoplasma gondii* shared symptoms suggest muscle cells and neurons are their chronic infection reservoirs

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A significant percentage of COVID-19 patients experience extended duration Long COVID [1, 2]. Several symptoms have been exhibited in Long COVID patients, such as mental dysfunctions (e.g., cognitive dysfunction, altered mental status, mental confusion or behavioral changes), neurological deficits (which along with depression, anxiety, memory and attention deficiencies, sleep disorders may alternatively be classified under mental dysfunctions), movement abnormalities (e.g., involuntary movements or ataxia/incoordination), fatigue, fever, dyspnea (labored breathing), myalgia (muscle pain), arthralgia (joint pain), tinnitus (ear ringing), vertigo (dizziness), otalgia (earache), anosmia (impaired smell), dysgeusia (impaired taste), speech and swallowing deficits and hair loss [1–4].

The primary aim of this letter is discuss some considerable similarities between the symptoms of Long COVID and the symptoms resulting from infections by the protozoan parasite *Toxoplasma gondii*. Table 1 provides a comparison of several potential symptoms that can result from infections by these pathogens.

Several Long COVID neurological symptoms could potentially be explained by cranial nerve (C.N.) infections affecting the functions of the 12 cranial nerves [4–6]. Another paper has proposed a link between Long COVID and the SARS-CoV-2 full spike protein through induced neuroinflammation [7]. Additionally, a study of SARS-CoV-2 antigens and cytokines from plasma samples extracted from 63 adults previously infected by SARS-CoV-2, including 37 adults diagnosed to have Long COVID/post-acute sequelae of COVID-19 (PASC), detected the SARS-CoV-2 full spike protein in 60% of individuals exhibiting Long COVID/PASC symptoms up to 12 months past their COVID-19 diagnosis [8]. This suggested to the researchers that there is a viral chronic infection reservoir for SARS-CoV-2, causing Long COVID/PASC in at least 60% of the cases [8]. However, the S1 and N proteins of SARS-CoV-2 were detected in fewer individuals and several inflammatory cytokine blood plasma levels were inconclusive [8]. The researchers hypothesized a viral reservoir of chronic infection and suggested that since Long COVID/PASC is a heterogeneous syndrome, that this could depend on the viral reservoir tissue location [8]. This raises several questions: (1) is there a viral reservoir causing 60% of the Long COVID/PASC cases, (2) where is the viral reservoir located and (3) are there are other pathways without a viral reservoir for the other 40% of the Long COVID/PASC cases?

The virus SARS-CoV-2 is not the only pathogen capable of chronic infections exhibiting numerous neurological and psychological symptoms. Protozoan parasites, including *Toxoplasma gondii*, cause chronic infections which in some cases can exhibit neurological and psychological symptoms that almost parallel Long COVID/PASC [6].

Since these pathogens are pervasive and adept intracellular pathogens, it is plausible that SARS-CoV-2 and *T. gondii* could in some cases use central nervous system neurons and/or muscle cells as chronic infection reservoirs. This could also explain the major similarities in these pathogens regarding the symptoms observed during their potentially chronic infections.

Long COVID/PASC symptoms also extensively match many of the symptoms caused by a partially or fully reactivated *T. gondii* infection [6]. Individuals infected by *T. gondii* can exhibit an extensive number of neurological and muscular symptoms, such as altered mental status, focal neurological deficits, mental confusion, cognitive dysfunction, ataxia, behavioral or psychomotor changes, involuntary movements, dyspnea, fevers, seizures, headaches, changes in

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Table 1 Compares the symptoms of Long COVID/PASC and *T. gondii* infections

The Major Exhibited Symptoms of Long COVID/PASC Compared to Infect. by *T. gondii*			
Exhibited Symptoms[1]	Long COVID	*T. gondii*	Alternative Category Or Possible Causation
Mental Dysfunctions[2]	Observed	Observed	cognitive dysfunction, altered mental status, mental confusion or behavioral changes
Neurological Deficits	Observed	Observed	mental dysfunctions?
Depression	Observed	Possible	a mental dysfunction?
Anxiety	Observed	Possible	a mental dysfunction?
Sleep Disorders	Observed	Possible	a mental dysfunction?
Movement Abnormalities[3]	Observed	Observed	involuntary moves or ataxia/incoordination
Fatigue	Observed	Observed	from chronic infection?
Fever	Observed	Observed	from chronic infection?
Hair loss	Observed	Possible	from chronic infection?
Dyspnea/Labored breath	Observed	Observed	from muscle cell infection?
Myalgia/Muscle pain	Observed	Possible	from muscle cell infection?
Arthralgia/Joint pain	Observed	Possible	from joint/muscle cell infection?
Tinnitus/Ear ringing	Observed	Possible	cranial nerve infection
Otalgia/Earache	Observed	Possible	cranial nerve infection
Vertigo/Dizziness	Observed	Possible	cranial nerve infection
Anosmia/Impaired smell	Observed	Possible	cranial nerve infection
Dysgeusia/Impaired taste	Observed	Possible	cranial nerve infection
Speech & Swallow Deficits	Observed	Possible	cranial nerve infection

[1][Refs 1–6]

[2]Mental dysfunctions include cognitive dysfunction, altered mental status, mental confusion or behavioral changes, neurologic deficits are perhaps a duplicated category; depression and anxiety could also be duplicated categories of mental dysfunctions

[3]Movement abnormalities include involuntary movements and ataxia/incoordination

vision, pneumonia, chorioretinitis and various cranial nerve infections [4, 6].

T. gondii has a documented capability to maintain chronic infections in muscles cells and central nervous system neurons with intracellular bradyzoite cysts [6]. Intracellular infections of cells typically lead to pathogen antigen presentation by the infected cells to CD8 T cells to induce cytotoxic CD8 T cell attacks to limit cellular infections [6].

However, neurons are known to be immuno-privileged to minimize damage from inflammation and other immune responses [9]. In addition, quiescent muscle cells, such as muscle stem cells, are also immuno-privileged with down-regulated antigen presentation [10]. Therefore, some adept pathogens would seek to evolve means to evade or disable CD8 T cells, such as *T. gondii's* use of metabolically inactive bradyzoite cysts in neurons and muscle cells, to evade cytotoxic attack by CD8 T-cells and maintain chronic infections [6].

Such chronic infections of neurons by *T. gondii* cysts can also potentially disrupt brain levels of neurotransmitters including glutamate, gamma-aminobutyric acid (GABA), and dopamine [6]. These disruptions can explain why latent *T. gondii* infections in some cases are linked to an extensive number of brain-associated disorders [6].

Coronaviruses, including the SARS-CoV-2 virus, can in some cases penetrate the blood–brain barrier (BBB), and/or utilize a neuronal pathway via sensory nerves (e.g., the olfactory nerve) or motor nerve endings [6]. The extent of transport of SARS-CoV-2 into the brain via the BBB or nerve pathways, can cause different infection pathways and consequences, and could potentially explain why Long COVID/PASC has widely varying sets of observed symptoms among individuals. There may also be other pathways without a chronic infection viral reservoir that could explain the remaining Long COVID/PASC cases that lack SARS-CoV-2 antigens.

In conclusion, the post-infection symptoms of Long COVID/PASC are sometimes experienced after active SARS-CoV-2 virus infections. Long COVID/PASC exhibits several neurological and muscular symptoms that substantially parallel *T. gondii* infection symptoms. *T. gondii* is known to use central nervous system neurons and muscle

cells to maintain chronic infections. It is therefore plausible that in some cases SARS-CoV-2 and *T. gondii* both use central nervous system neurons and muscle cells as reservoirs to maintain chronic infections. There may also be other pathways without a chronic infection viral reservoir that could explain the remaining Long COVID/PASC cases that lack SARS-CoV-2 antigens.

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Declarations

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