Short Communication

The Pathogenesis of Neurological Disorders and Brain Fog in Post-COVID19 Syndrome (PCS)

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Abstract:

Since the pandemic and then now since vaccination, many new signs and symptoms are being observed symptoms of long COVID. In spite of the fact that most individuals with COVID-19 get better within weeks of their sickness, but a small numbers of individuals encounter "Post-COVID" conditions. This is called "long COVID" syndrome if these remain with symptoms after four weeks of first being infected with "SARS-CoV-2", that causes "COVID-19". Most common long COVID symptoms, include brain fog, fatigue, anxiety, and depression are important symptoms experienced by Post-COVID-19 patients. The patients are divided into 2 groups, the Post-COVID-19 patients, for up to 4-12 weeks following the infection, and Post-COVIC-19 Syndrome (PCS) for more than 12 weeks.

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Neurological complications like headache, brain fog, fatigue, cognitive impairments, taste, flavor, sleep and mood disorders, delirium, stroke etc, are more common in critically ill patients with long COVID-19. There could be the multiple causes due to multisystemic disorders with a wide spectrum of clinical personations.

There are many questions, those come in our brain, are these conditions may be due to the persistent virus or slow clearance of **SARS-CoV-2**? are these because of the immune cell mutation after the attack of virus? Are these because of autoimmune response due to molecular mimicry? Are these being due to activation of other viruses like Epstein Bar Virus (EBV)?, are these being due to decreased in blood flow to brain or due to direct infection of the brain tissue?, are these clinical manifestations being due to damage of the endothelium of the blood vessels? Why the neurological symptoms are more common in females which also aligns with more immune system issues in women, hence, it is possibly the immune system vs., endothelial damage.

In these patients, the anosmia, may be due to involvement of olfactory system and reduction in glymphatic system function of the brain parenchyma. These results are due to accumulation of waste products and inflammatory cytokines in the brain parenchyma which are not properly drained from the brain. The accumulated fluid causes the long hauling and leading to the neurologic symptoms like depression, fatigue, myalgia and brain fog etc[1].

In a study was conducted on 100 consecutive patients of long covid presenting to the Neuro clinic between May and November 2020. The mean age of these patients was 43.2 years (±11.3 years; n = 100) and 70% were women and 48% were evaluated using telemedicine. The most common comorbidities were depression/anxiety (42%) and autoimmune disease (16%). The study shows that brain fog was more commonly seen in females[2].

In another study, characterizing to long COVID in an international cohort of 7 months on 3762 participants

from 56 countries, almost similar findings were seen[3].

Pathogenesis of Long Haulers and Brain Fog

These **long haulers** were consequence of severe disease only. The laboratory records of these patients showed persistent high level of TNF-alpha, IL-6, and IL-8 during their sickness[3].

There was also a low count of CD8 cells in such along haulers after **COVID** attack. A high level of CCR5 receptors were also reported on T cells of these patients which may help the virus to attach to these receptors like HIV and facilitates these T cells to reach the site of inflammation[2,4].

The brain fog may happen due to many reasons, may be due to presence of virus and their direct cytopathic effect or due to immune system dysregulation or due to endothelial damage of the blood vessels leading to the hypoxia of the brain. This results in a low blood supply and metabolic de-arrangement. There may be myelin sheath damage in such patients which feel neurological symptoms. This pathogenesis may be when the virus had ended in the brain tissue after infection of SARS-CoV-2.This may be for the following reasons.

1. It may be due to oversensitivity of the immune system, microglial activation with microglial nodules, and destruction of neurons.
2. It may be due to the slow clearance of the virus which infects the monocytes at a large level which delays the recovery of the patients from the post-covid syndrome.
3. ACE-1/ACE-2 imbalance leads to grave consequences.
4. Disruption of glymphatic, failure in the cleansing system of wastes and proinflammatory cytokines.
5. Damage of blood-brain barrier due to cytokine storm.
6. Damage by mimicry or tissue-mimicking effect of autoantibodies.
7. This may be due to other viruses sitting around and are being reactivated e.g, EBV, which in turn can cause fatigue.

Main symptoms of Long Haulers:

There are more than 200 symptoms but the followings are the most common symptoms

1. Chill
2. Sweat
3. Respiratory symptoms
4. Cough and breathlessness.
5. GIT issues
6. Fatigue
7. Post exertional malaise
8. Neurological symptoms (Brain fog, recalling loss, cognitive loss, myalgias, encephalopathy, headache, anosmia, ataxia, seizures, anosmia, and stroke in some patients.
9. Body aches

Why brain fog, myalgia, fatigue, depression after COVID-19[4,5]:

It is the state of confusion when you are not fully alert and engaged (Figure 1), there may be a reduction in Glymphatic system function, or an ongoing inflammation in the brain, or decreased blood flow to the brain, or an autoimmune condition in which the body makes antibodies that attack the brain or several of these abnormalities. It is still not clear but any of the above mechanisms may be responsible for this outcome. There are four fluids in the brain, like

1. Intracellular fluid
2. Interstitial fluid bathing the neuron
3. Blood in the blood vessels
4. **CSF** is formed by the choroid plexus by ultrafiltration of blood and circulates in a closed system of two lateral ventricles, 3rd ventricle, and 4th ventricle. From the fourth ventricle, it goes to subarachnoid spaces. From these meninges, the **CSF** goes back to venous sinuses.

What is the Role of Glymphatic in the Brain?

From the arachnoid space, arteries pass to the brain tissue. A system of connecting perivascular spaces is called the **Glymphatic system**. These spaces are a continuation of **CSF** loops around the arteries and **CSF** also flows to these spaces from arachnoid spaces to these lymphatics.

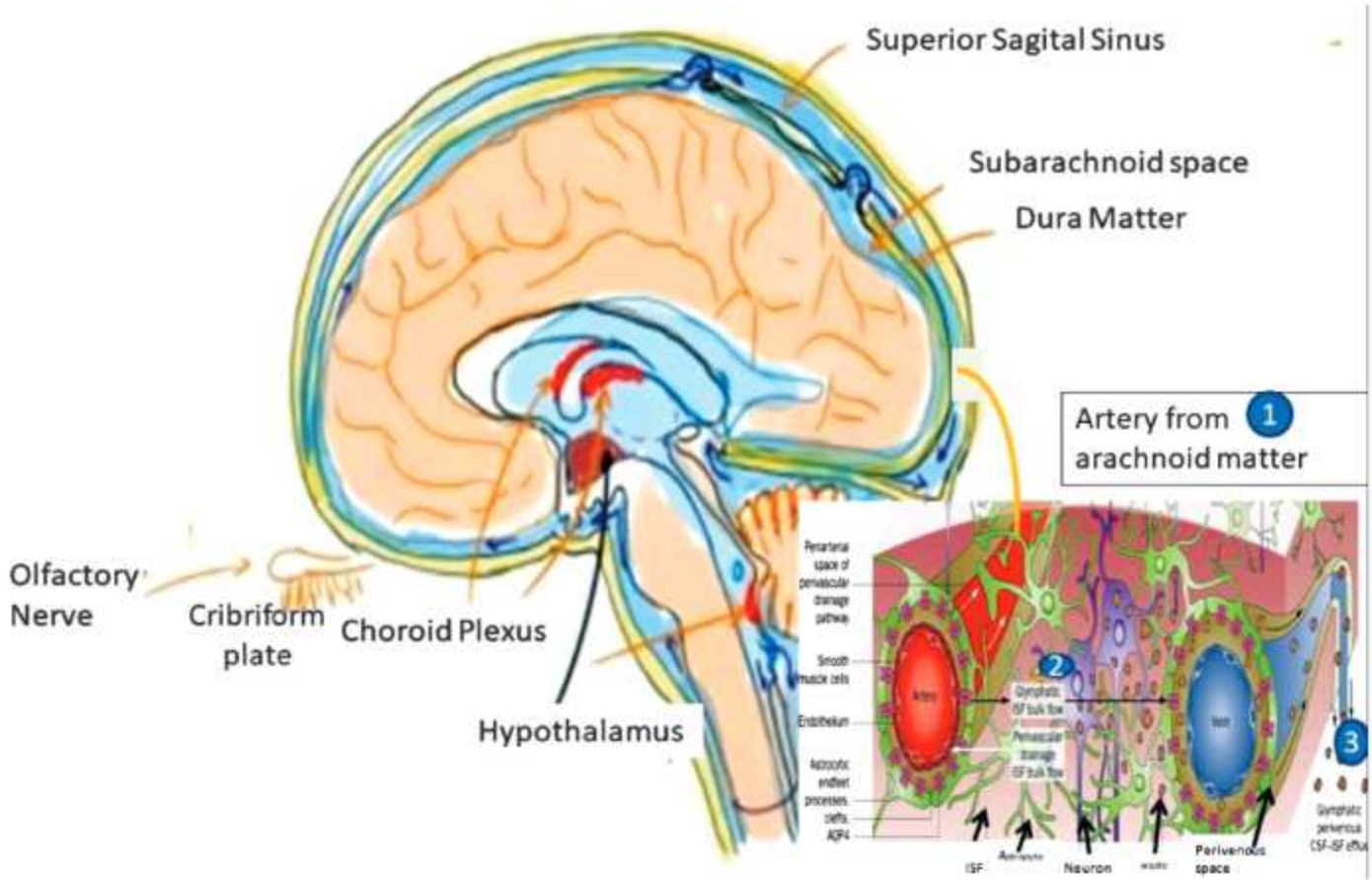

Figure 1: *Diagrammatic illustration of the perivascular clearance system which comprises perivascular drainage and glymphatic pathways*[9].

When these spaces are filled, the **CSF** starts oozing out slowly from the peri-arterial spaces to the brain tissue. Outside, the blood vessels and these spaces are blood-brain barriers formed by the foot processes of the astrocytes. But there are micro-channels, called aquaporins (AQPs) from them the **CSF** oozes out, towards interstitial fluid to bath the neurons and other important brain cells. **AQPS** are water channel proteins that increase cell membrane water permeability and assemble in cell membranes as tetramers. The fluid washes all the metabolic ends products, and if there is any inflammation, the inflammatory cells, debris, or any injurious agent present around the neurons towards the venous system. In other words, it is a beneficial system in the brain to remove the unwanted material from the brain. There is a strong BBB and without this lymphatic system, brain cells could be damaged by these metabolic end products or if there is any inflammation, the inflammatory cytokines. So, these are washed by this fluid from here to perivenous spaces towards the cervical and olfactory lymphatic system.

The problem in long haulers is disruption of this lymphatic system and the inflammatory end products are not washed out and start compression on the neurons resulting in brain fog. The majority of the drainage is near the olfactory nerves and in **COVID19**, this nerve is inflamed, therefore, the nerve responsible for smell gets affected. This blocks the lymphatics and stops the drainage of fluid to the venous sinuses. As a result, the fluid accumulates in the brain including all the debris, metabolic end products, and inflammatory mediators. The waste products are not washed out as a consequence causing brain fog[9,11].

CSF flow through the Glymphatic system.

It is a step-wise process shown in figure 1 and described below. Their blockage causes backpressure and consequences in the long haulers.

1. **CSF** flows into the brain parenchyma via the peri-arterial space, surrounding the parenchymal arteries and enters the interstitium of the brain tissue via aquaporin 4 (AQP4) which are controlled water

channels. These are distributed in the end feet of astrocytes which strengthen the outer walls of the perivascular spaces and becomes the interstitial fluid (ISF).

2. **CSF** entering the **ISF** flows by convection and exchange occurs within the brain parenchyma.
3. After bathing the waste products, debris from the brain tissues, it flows into the perivenous space, which is the peri-vascular space around the deep-draining vein, and is subsequently discharged outside the brain through venous system.

These end products, affect the hypothalamus, causing fever and mental confusion. Loss of sensation and disturbance or emotional system (three main jobs of this area are Control of temperature, sensation, and emotion). So, the patients develop fatigue, myalgia, and fever.

How to fix the Brain fog problem

1. Massage around central lymphatic drainage along the bilateral cervical neck areas.
2. By moving the neck and spinal cord to increase spinal drainage causing the pumping effect on the lymphatics helps in pushing out the blocked **CSF**.
3. If you sleep well, it reduces the neurotransmitters like Epinephrine and NEN during sleep and helps in reducing the compression effects on the neurons.
4. The brain lymphatic system only operates during sleep.
5. The longer you are awake, the more products are accumulating in the brain.
6. Epinephrine and Norepinephrine cause neurons to make more alert and increase their metabolism, their size is a little bit increased. These neurotransmitters also reduce the activities of blood vessels and reduce their pumping effect.
7. During sleep when these neurotransmitters are reduced, the neurons go on rest with low metabolic activity, and the activity of blood vessels is increased which allows more lymphatic drainage from the brain to the venous system.
8. If there's an infection, the cytokines are not drained properly and accumulate in the braining, resulting in brain fog.
9. During sleep the "**CSF**" production is increased due to more activity of the blood vessels and choroid plexus causing a reduction in brain fog, more the production more the activity of the lymphatics which washes out the debris, metabolic end-products, and cytokines
10. Sleeping better is for all of us, especially if anybody has "**COVID19**" to wash out all the metabolic end-products
11. Consult the Neuro physician
12. Reassurance
13. Use melatonin as it is not only a prophylactic measure for **COVID19** but also causes you to sleep well

Conclusions:

The **COVID** Pandemic has become an alarming global health issue because it has several new and unfamiliar features. It has shown multisystemic demonstration from **"SARS-CoV-2"** respiratory to Renal, GIT, Cardiac, and Neurological manifestations through interaction with the central nervous system. The Post long COVID-19 has a wide spectrum of neurological disorders due to many reasons, some of them are due to multisystemic damage and others are due to immune dysregulation or thrombotic disorders caused by vascular damage. The authors have mentioned very few neurological complications.

Long COVID or long haulers of "**PCS**", is becoming a new entity after the diagnosis of "**SARS-CoV-2**" when the clinical manifestations are prolonged more than 4 weeks of initial symptoms. There may not be a single cause of "**PCS**", but because of the multi-systemic involvement and persistence of low-grade inflammation, immune mediated vascular dysfunction, which may play a key role in its pathogenesis of the neurological complications.

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