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BRAIN FOG IN POST-COVID SYNDROME: MECHANISMS OF MICROCLOT FORMATION, BBB DISRUPTION, AND NEUROINFLAMMATION

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ABSTRACT

Background: Post-COVID syndrome (PCS) is characterized by persistent symptoms following infection, most notably "brain fog." Affecting approximately 5-15% of individuals in recent vaccinated cohorts-and up to 30% in early pandemic studies-brain fog significantly impairs professional, educational, and daily functioning. Its underlying biological mechanisms remain unclear, partly due to heterogeneous case definitions and study designs.
Methods: We conducted a narrative, hypothesis-driven review of PubMed, Web of Science and Scopus from 2019 to January 2026, focusing on human mechanistic studies of PCS-related cognitive dysfunction.
Findings: Several human cohorts describe persistence of SARS-CoV-2 spike antigen in plasma months after infection. Studies associate this with three overlapping pathways: (1) formation of fibrin amyloid microclots with impaired fibrinolysis in vitro; (2) increased blood-brain barrier permeability linked to elevated MMP-9 and oxidative stress markers in blood and CSF; and (3) sustained microglial and astrocytic reactivity with elevated cytokines. Evidence is largely cross-sectional and mechanistic data derive mostly from small studies. The specificity and causal role of microclots in post-COVID syndrome remain contested in recent reviews.
Interpretation: We outline a testable integrative model in which microvascular injury, blood-brain barrier disruption and neuroinflammation may contribute to persistent cognitive symptoms in PCS. The model remains hypothetical, as current data are largely cross-sectional and derive partly from in vitro work. Longitudinal studies with biomarker stratification are needed before mechanism-based interventions can be evaluated.

KEYWORDS

Post-COVID Syndrome; Brain Fog; Blood-Brain Barrier; Neuroinflammation; Microclots; Fibrin Amyloid

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Introduction

Brain fog, marked by cognitive impairment, mental fatigue, concentration difficulties and slowed processing, has emerged as a prevalent and debilitating symptom of Post-COVID Syndrome (PCS), also termed long COVID or post-acute sequelae of SARS-CoV-2 infection (PASC). The World Health Organization (WHO) defines PCS as symptoms persisting beyond 3 months after SARS-CoV-2 infection that cannot be explained by alternative diagnoses. Early pandemic cohorts reported persistent cognitive symptoms in 20-30% of infected individuals [2][3][4]; more recent population-based studies in largely vaccinated cohorts suggest lower estimates of approximately 5-15%, indicating heterogeneity by vaccination status, study period and case definition. Brain fog encompasses deficits in attention, executive function and memory that impair performance of complex tasks.[1][5].

The consequences extend beyond the patient. Cohort studies report lost workdays, higher use of primary care and lower quality-of-life scores. Because the underlying biology remains unclear, current care is limited to symptomatic treatment and rehabilitation [2][3][4][5].

Recent research points to several overlapping mechanisms rather than a single cause. Human studies link cognitive symptoms to vascular changes, blood-brain barrier leakage and persistent inflammatory signalling that may reinforce one another:

Human studies to date point most consistently to three processes that often co-occur in PCS: (1) microvascular changes, including fibrin amyloid microclots observed mainly in vitro that may reduce capillary flow; (2) blood-brain barrier leakage with increased passage of cytokines and immune cells into the CNS; and (3) sustained activation of microglia and astrocytes with altered cytokine signalling. Researchers find persistence of viral spike protein and systemic inflammatory signals as upstream triggers, but their contribution in the human body remains uncertain.[2][4][5][8][10][11][12][13][15]

These processes may interact, but current data are largely cross-sectional and do not establish a causal loop. Research examine the evidence for each process in PCS-related brain fog, considers how they might relate to one another and highlights where longitudinal human data are lacking.

Mechanisms of Brain Fog Pathophysiology

Microclot Formation and Fibrin Amyloid Pathology

In vitro studies report that fragments of the SARS-CoV-2 spike protein can alter fibrin behaviour. Researchers examined two peptides in detail: residues 601-619 (Spike601) bind fibrinogen and slow thrombin-mediated clot formation, while residues 685-701 (Spike685), located near the furin cleavage site, form fibrils that resist plasmin digestion in purified systems. Other groups described similar amyloidogenic regions under different names.

Translation to patients remains uncertain. A 2024 review concluded that circulating particles described as 'fibrinaloid microclots' are not unique to PCS, do not meet standard criteria for true clots and have not been linked causally to symptoms. Most mechanistic data are limited to cell-free assays, and independent replication in large clinical cohorts is lacking.[6][7][8]

In vitro work reports that spike protein amyloid fibrils disrupt fibrinolysis through several mechanisms: direct resistance to plasmin-mediated breakdown, formation of dense fibrin networks with altered morphology, and sequestration of fibrinogen that reduces its availability for normal clotting. Researchers linked these changes to clots that resist proteolytic breakdown in cell-free assays.

The pathological clots reported in PCS patients have distinct characteristics that may contribute to their pathophysiological impact:

- Size: Variable, typically reported as 1-200 μm in the literature, which would exceed the diameter of cerebral capillaries (typically 5-10 μm). This discrepancy raises questions about in vivo trapping sites and physiological relevance.
- Composition: Misfolded amyloid forms of fibrinogen (fibrinaloids) reported to entrap α-2-antiplasmin, inflammatory cytokines and chemokines, and other plasma proteins. Some studies suggest detection of viral proteins, but findings remain inconsistent.
- Properties: Resistance to proteolysis attributed to amyloid structure and incorporation of fibrinolysis inhibitors; a proposed prothrombotic effect; slow release of entrapped inflammatory mediators; and possible local oxidative stress. These features derive mainly from ex vivo staining and their clinical relevance remains uncertain.[6][9]

Authors propose that microclots obstruct capillaries, which could lead to intermittent hypoperfusion in affected territories. Watershed areas and regions with high metabolic demand have been suggested as particularly vulnerable, though direct in vivo evidence is lacking. Endothelial dysfunction has also been hypothesized to result from mechanical effects, ischemia-reperfusion injury, contact with amyloid surfaces, or release of entrapped inflammatory molecules, potentially increasing permeability, leukocyte adhesion, and procoagulant activity.[9]

In some PCS cohorts, researchers reported higher D-dimer levels and reduced fibrinolytic capacity alongside greater symptom severity and exercise intolerance. Microclot burden has also been reported to correlate with cognitive symptoms and post-exertional worsening.

It is proposed that microclots promote BBB disruption through endothelial injury and oxidative stress, possibly involving MMP activation and tight junction loss, and through release of trapped cytokines such as TNF-α, IL-1β and IL-6. They also link to neuroinflammation via systemic thromboinflammatory signals, microvascular injury, oxidative stress that may engage NF-κB and NLRP3 pathways, and release of DAMPs from ischemic tissue.

The study suggests bidirectional interactions: BBB leakage may favour a prothrombotic endothelial phenotype, while neuroinflammation may increase tissue factor expression and platelet activation. Whether these interactions form a sustained cycle in patients has not been demonstrated.[6][9][10]

SARS-CoV-2 Persistence in CNS and Brain Tissue

Autopsy studies detected SARS-CoV-2 in CNS tissue, but the available data come from a small cohort of fatal acute COVID-19 cases, not from PCS survivors. In a study of 44 deceased patients, viral RNA was found in CNS tissue in 90.9% of cases, with persistence up to day 230 post-symptom onset.[11] Regional tropism was observed (hypothalamus and cerebellum early; cervical spinal cord and basal ganglia late), and evidence of possible active replication included subgenomic RNA, a single successful virus isolation from the thalamus, and minor spike gene variants. Notably, despite widespread viral RNA detection, overt histopathological changes were largely absent, suggesting that any neurological effects may involve functional disruption rather than gross tissue destruction. Viral clearance appeared less efficient in non-respiratory tissues, including the CNS, in late illness (≥31 days) compared to early illness.

Mechanisms of Blood-Brain Barrier Disruption

Several biomarkers provide indirect evidence of BBB compromise in COVID-19 patients with neurological manifestations and help link peripheral measurements to CNS processes.

MMP-9 levels are elevated in patients with neurological complications compared to those without, with levels tracking severity over time. Brain pericytes at the neurovascular unit can rapidly release MMP-9 in response to inflammatory stimuli. SARS-CoV-2 has been reported in vitro and in severe acute disease to infect brain microvascular endothelial cells and may cross the BBB via MMP-9-mediated disruption of the basement membrane.[12]

Clinicians utilize blood GFAP as a marker of BBB disruption and astrogliosis, given that its levels are elevated in COVID-19 and correlate with disease severity.

The levels of neurofilament light chain (NfL), a marker of axonal injury, are highest among patients with neurological manifestations.

PPIA (cyclophilin A) peaks in ICU patients during acute illness and has been linked to MMP-9 induction via CD147 in an NF-κB-dependent pathway.

Important caveat: These biomarkers are elevated in many neurological conditions beyond PCS, including stroke and traumatic brain injury, and are confounded by age and renal function, limiting their specificity for PCS-related BBB disruption. Elevated levels indicate BBB compromise but cannot distinguish PCS from other causes without clinical correlation. Notably, these data derive from hospitalized patients during acute illness; applicability to outpatient PCS brain fog is uncertain.

Researchers propose the MMP-9 pathway in BBB disruption: pericytes can release MMP-9 in response to inflammatory signals, MMP-9 may degrade tight junction proteins and basement membrane laminin and the result may be increased permeability and leukocyte adhesion.

The PPIA-CD147-MMP-9 signaling axis has been proposed to link SARS-CoV-2 to BBB disruption: spike protein can bind CD147 on endothelial cells and pericytes, PPIA may facilitate this interaction and downstream NF-κB activation can promote MMP-9 and cytokine release. In preclinical models, anti-CD147 antibody reduced cytokine responses.

Oxidative stress may contribute through several routes: ROS can modify tight junction proteins and activate latent MMP-9, NF-κB signaling may increase cytokine production, reduced nitric oxide bioavailability may promote inflammation, and fibrin amyloid microclots have been proposed to induce oxidative stress via ischemia-reperfusion injury.[12][10]

Reported cellular changes include pericyte dysfunction with MMP-9 release, swelling and detachment of astrocytic end-feet that compromise BBB integrity, and endothelial apoptosis with reduced tight-junction expression.[12]

Complement activation through classical, lectin and alternative pathways can promote BBB disruption, with C3a and C5a increasing vascular permeability and driving leukocyte recruitment.[13]

Higher CSF-to-serum ratios of S100B, GFAP and NfL indicate BBB disruption and CNS injury. MRI studies have reported microbleeds and white matter hyperintensities that correlate with cognitive deficits.[12][14]

BBB leakage may allow microclot-associated inflammatory molecules to reach the CNS and could facilitate viral entry. Bidirectional interactions have been suggested, in which neuroinflammation may worsen BBB integrity through ROS and MMP activation, and microclots may increase permeability via endothelial injury.[10][12]

Neurological Manifestations and Cognitive Dysfunction

Brain fog includes deficits in attention, processing speed, executive function and memory. It affects a notable minority of PCS patients and is often worsened by exertion (PESE). Neurological assessments have documented objective cognitive deficits, neuropsychiatric symptoms and in some cases peripheral neuropathy or cerebrovascular findings.[2][5][12]

MRI studies have shown accelerated volume loss, particularly in olfactory-related regions and prefrontal cortex. These changes can persist at 6-12 months, suggesting longer-term structural effects. Functional MRI has shown altered connectivity within default-mode and executive-control networks. MRS studies report reduced NAA, consistent with neuronal dysfunction and elevated myo-inositol, consistent with glial activation.[14][12]

Elevated blood markers point to neuronal injury (NfL), astrocytic involvement (GFAP) and systemic inflammation.[12]

Microvascular ischemia linked to microclots may impair neuronal function, BBB disruption may permit entry of inflammatory mediators, and neuroinflammation may affect neurotransmitter signaling. These mechanisms have been proposed to converge on key neural networks and contribute to brain fog.[10][12][14]

Neuroinflammatory Pathways and Cytokine Dysregulation

Persistent viral antigens may activate microglia through Toll-like receptors, promoting proinflammatory polarization, ROS production and cytokine release. Reactive astrocytes can show GFAP upregulation and reduced glutamate uptake, which may amplify neuroinflammation.

Microglial activation is considered a hallmark of neuroinflammation in PCS. Studies point to maladaptive activation with a sustained proinflammatory phenotype. Effector mechanisms include release of proinflammatory cytokines, ROS and complement components. Studies report elevated CSF cytokines.

Astrocytic reactivity involves morphological and molecular changes, including increased GFAP expression. In chronic inflammation astrocytes may exert both protective and detrimental effects.[12]

Activation of brain microvascular endothelial cells can increase adhesion molecule expression, promoting leukocyte adhesion and cytokine production.[10]

Pericyte activation at the neurovascular unit may involve MMP-9 production, secretion of inflammatory mediators and loss of BBB-supportive functions.[12]

When BBB integrity is compromised, peripheral immune cells may enter the CNS. Monocytes can differentiate into microglia-like macrophages, T lymphocytes may infiltrate and release cytokines and neutrophils can release MMP-9 and ROS.[12]

Authors propose that elevated CNS cytokines disrupt neurotransmitter systems and impair synaptic plasticity.[13]

Key molecular pathways include:

- NF-κB Pathway: Activated by oxidative stress and cytokine signaling, driving proinflammatory gene expression. In PCS, this pathway is activated by microclot-induced endothelial damage and persistent viral antigens [10][12][15].

- NLRP3 Inflammasome: DAMP accumulation activates NLRP3, promoting IL-1β release [16]. While fibrin amyloid microclots and spike protein are proposed as PCS-relevant DAMPs [6][9], direct evidence in PCS patients remains limited.

- Complement System: C3a and C5a enhance neuroinflammation and synaptic elimination [17]. Elevated C3a/C5a levels in serum and CSF of COVID-19 patients [13] suggest potential complement activation in PCS.

- JAK-STAT Pathway: IFN-γ signaling through JAK-STAT promotes chronic inflammatory gene expression.

Neuroinflammation may amplify BBB disruption and persistent viral antigens and microclot-derived mediators may drive it.[10][12][13][15][16][17]

Relationship Between Peripheral Inflammation and CNS Effects

The relationship between peripheral inflammation and CNS effects in PCS is characterized by complex bidirectional communication pathways.

For humoral signaling, soluble factors from the periphery signal to the brain through multiple mechanisms: cytokines bind to receptors on cerebral endothelium, triggering secondary messenger release; cytokines activate afferent vagal signaling; immune cells traffic across the BBB; and cytokines may passively diffuse across regions with weaker BBB protection [12].

During cellular trafficking, immune cells can also reach the brain directly. Both monocytes and T cells are able to cross from the periphery into the CNS, where they release cytokines and chemokines.[12]

With neural pathways, the peripheral nervous system also signals inflammation to the brain, mainly through vagal, trigeminal and spinal afferents.[18]

In the case of metabolic factors, other peripheral contributors include dysregulation of the HPA axis and disturbances in mitochondrial function.[18]

As for CNS-to-periphery signaling, this communication works both ways. CNS inflammation can shift HPA-axis activity and autonomic balance, which in turn affects heart rate and immune responses.[18][19]

When spike protein remains detectable in the circulation, it can sustain ongoing immune stimulation.[10] Higher levels of circulating inflammatory markers have been linked to greater severity of cognitive symptoms [4][10][11][12].

Discussion

We propose that a self-reinforcing loop involving microclot formation, BBB disruption and neuroinflammation, possibly sustained by persistent SARS-CoV-2 antigens, may help explain the chronicity and heterogeneity of brain fog in PCS (Figure 1) [1-17].

Figure 1. Integrated Pathophysiological Model of Brain Fog in Post-COVID Syndrome.

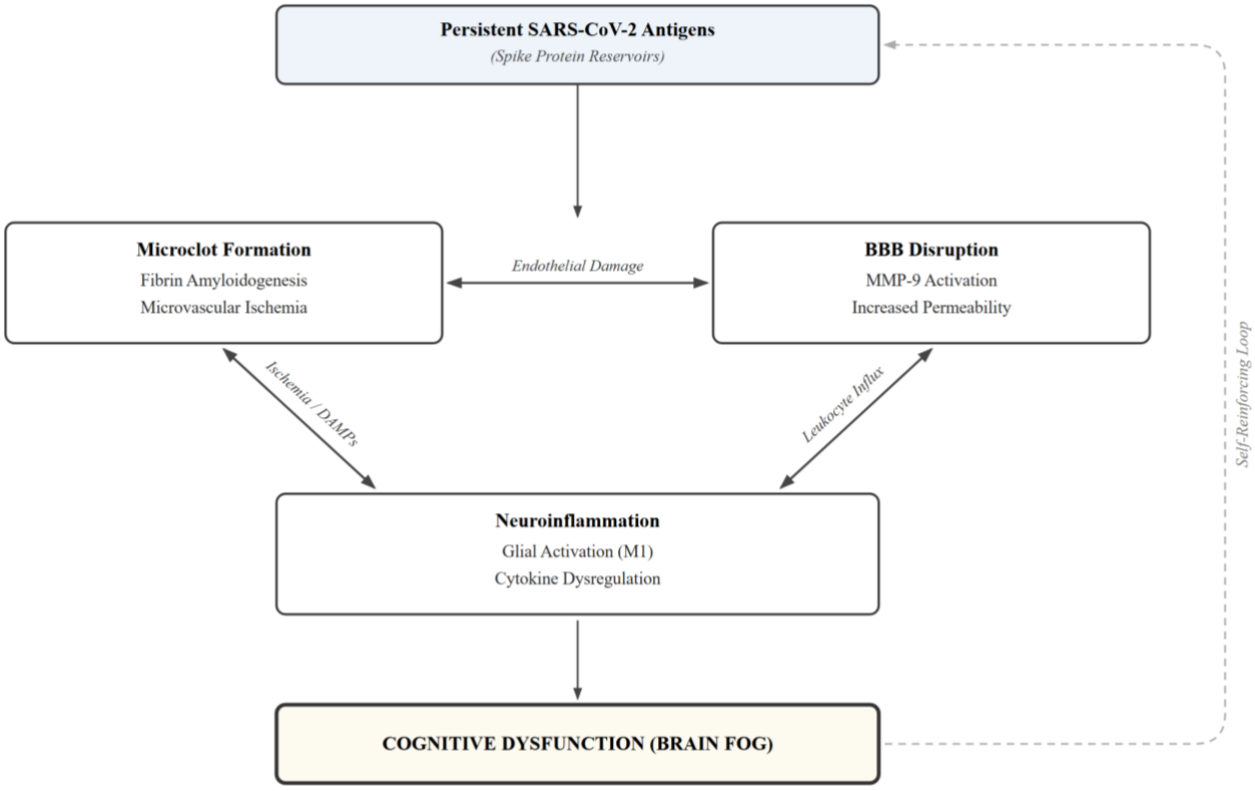

Fig. 1. *Hypothetical model of brain fog in PCS. Persistent SARS-CoV-2 antigens are shown in relation to three processes described together in the literature: (1) microclot formation through fibrin amyloidogenesis, (2) BBB disruption linked to MMP-9 activity, and (3) neuroinflammation with microglial activation and cytokine release. Arrows indicate proposed interactions, not proven causality. BBB, blood-brain barrier; MMP-9, matrix metalloproteinase-9.*

Several other mechanisms have also been proposed, and they are not mutually exclusive with this model. Autoimmunity linked to molecular mimicry could generate autoantibodies that target neural tissue. Mitochondrial dysfunction after SARS-CoV-2 infection may lower ATP availability and contribute to cognitive symptoms. Dysautonomia, including POTS, is common in PCS and may reduce cerebral perfusion.

Clinical implications:

For diagnostics, panels that combine coagulation markers such as D-dimer and fibrinogen with BBB markers such as MMP-9 and GFAP and with neuroinflammation markers such as NfL and cytokines could help define patient endotypes. For therapy, approaches that target fibrinolysis remain experimental. Current trials do not support routine use of fibrinolytics in PCS, and the bleeding risk means guidelines do not recommend them outside clinical studies. Strategies aimed at the BBB or at neuroinflammation are still largely preclinical, and antiviral treatments for persistent antigen have shown mixed results. For rehabilitation, the best-supported options remain cognitive rehabilitation combined with pacing and measures that improve autonomic regulation, for example vagal stimulation.[8]

Future work should address four areas. First, develop sensitive methods to detect microclots and viral persistence in vivo. Second, use longitudinal designs to test temporal order and causality. Third, evaluate mechanism-based treatments in trials that stratify by biomarkers. Fourth, compare findings with other post-viral syndromes.

Conclusions

Brain fog in PCS appears to result from several interacting processes, including microclot formation, BBB disruption and neuroinflammation, possibly sustained by persistent SARS-CoV-2 antigens. This integrated view helps explain why symptoms vary between patients and why treatment remains difficult. In practice, effective care will probably need to address more than one mechanism at a time, with the choice of therapy adapted to each patient's endotype.

Conflicts of Interest: No conflicts of interest to declare.

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