



NEUROINFLAMMATION IN ALZHEIMER'S DISEASE AND COVID-19 CAN CAUSE BRAIN FOG

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ABSTRACT

Brain fog is a predominantly functional and often reversible cognitive impairment that can be caused by brain infection, stress, or other conditions, and primarily results from neuroinflammation and synaptic dysfunction. It is characterized by mental confusion, difficulty concentrating, slowed thinking, and short-term memory problems, and is associated with numerous neurological and systemic conditions, is often treatable, and is more common in older adults and in some viral brain infections. Inflammation is a key driver of brain fog in coronavirus disease 2019 (COVID-19) and Alzheimer's disease (AD). The systemic immune response in COVID-19 and neuroinflammation, fueled by the passage of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) across the blood-brain barrier (BBB), are associated with cognitive and neurological symptoms such as memory problems, headaches, and loss of smell. Furthermore, the virus can increase the permeability of the BBB, allowing harmful inflammatory molecules to enter the brain and contribute to the persistence of neurological symptoms even years after infection. In Alzheimer's disease (AD), cognitive decline is progressive and irreversible due to the accumulation of β -amyloid and tau, the loss of synapses and neurons, and chronic neuroinflammation. In AD, persistent activation of microglia and inflammatory mediators accelerates neurodegeneration and disease progression. Although early-stage AD and brain fog share neuroinflammatory mechanisms, AD progresses to an irreversible pathology mediated by β -amyloid and tau with synaptic and neuronal loss, while brain fog is primarily a functional, inflammation-driven condition, with largely preserved neurons.

KEYWORDS: *Neuroinflammation, brain fog, viral infection, SARS-CoV-2, COVID-19, Alzheimer's disease, inflammatory mechanism*

INTRODUCTION

Brain fog is a cognitive impairment that can appear in numerous neurological conditions and is characterized by mental confusion, deficits in attention, verbal and non-verbal learning, slowed processing and motor functioning, and short-term memory problems.

Brain fog results from cardiovascular, neural, metabolic and immune function impairments and occurs in some diseases involving the nervous system, such as Parkinson's disease (PD) and Alzheimer's disease (AD), various forms of dementia, head trauma, epilepsy, brain tumors, migraines, encephalitis, stroke, and central nervous system (CNS) inflammation (1,2). Brain fog can also appear in other conditions, including fibromyalgia, long coronavirus disease, chronic fatigue syndrome, anemia, and some autoimmune diseases such as systemic lupus erythematosus (3,4) and has

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been reported in individuals suffering from depression, anxiety, diabetes, vitamin B12 or iron deficiency, sleep disturbances, hypothyroidism, fatigue, and side effects of certain medications (antihistamines, antidepressants, etc.) (5,6). Brain fog can last for weeks or months, appear suddenly, and cause severe headaches, difficulty speaking, impaired consciousness, weakness, and seizures (3). Brain fog can be constant or intermittent and can progressively worsen; however, it is treatable (7).

In AD, there is irreversible neuroinflammation due primarily to the accumulation of β -amyloid and tau protein that damage neurons, while in coronavirus disease 2019 (COVID-19), inflammation is induced by systemic vascular infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which may be reversible. However, neuroinflammation, blood-brain barrier (BBB) dysfunction, microglia, and vascular alterations occur in both diseases. In viral infections such as COVID-19, disruption of the BBB and neuronal infection promote neuroinflammation and cognitive symptoms, while in AD, persistent activation of microglia and inflammatory mediators accelerates neurodegeneration and disease progression.

Early-stage AD and brain fog share neuroinflammatory mechanisms, however AD is a progressive, irreversible neurodegenerative disease mediated by β -amyloid and tau with synaptic and neuronal loss, while brain fog is primarily a functional, often treatable condition with largely preserved neurons that is driven by inflammation.

BRAIN FOG AND INFLAMMATION

Inflammation is undoubtedly a major factor in brain fog. Scientific evidence indicates that neuroinflammation in individuals with COVID-19 leads to neurological symptoms such as memory problems, headaches, loss of smell, and others (3). COVID-19 can cause damage to brain tissue, resulting in multisystem inflammatory syndrome (3). In this disease, neuroinflammation is triggered by SARS-CoV-2 crossing the BBB which, over time, can induce a chronic form of long COVID that causes brain fog (3). Potentially, any inflammatory molecule crossing the BBB can cause this symptom. The cognitive symptoms that appear in CNS infection can be explained, at least in part, by brain inflammation induced by the virus crossing the BBB (8).

In viral brain infections, inflammation is the most important reaction linked to cognitive symptoms and is responsible for neurological problems (9). Inflammation occurs when immune cells react against foreign substances invading the body. In the case of SARS-CoV-2 invasion, a systemic immune response occurs that also involves the brain (3). SARS-CoV-2 rarely infects the brain directly, but in full-blown disease, brain immune activity is very high and is usually most evident in the olfactory bulb and brainstem, which control the respiratory system (10). These effects have been noted in people who died after SARS-CoV-2 infection (11). In these systemic cases of infection, specific brain areas present a more evident immune reaction, with consequent cerebral symptoms (11). Unresolved neuroinflammation can lead to neurological symptoms caused by long-term COVID-19, which can persist even years after the first viral infection (12,13).

Viruses, including SARS-CoV-2, can cause damage to the BBB by making it more permeable, which allows the passage of harmful substances to the brain, an effect that would be impossible with an intact BBB (14). So, in long-term COVID-19, as the BBB is disrupted, inflammatory immune cells can pass into the brain causing brain fog with concentration and memory problems. Inhibition of inflammation may protect the brain from SARS-CoV-2 viral infection (10.1002/biof.1726). Brain samples from people who died from COVID-19 revealed that SARS-CoV-2 binds to dopaminergic neurons and infection can cause the release of inflammatory molecules that causes damage (15,16).

In AD and PD, brain fog results from molecular and cellular alterations that compromise the functioning of neuronal networks, often before neurons die (17). Initial cognitive impairment is therefore primarily a problem of synaptic dysfunction, followed by neurodegeneration. In neurological diseases, such as AD and PD, there are a loss of cholinergic neurons in the basal nucleus of Meynert, resulting in a decrease in attention span, episodic memory, processing speed, and acetylcholine levels, symptoms that contribute significantly to brain fog (19).

Brain fog can appear in the early stages of AD (20). The main difference between brain fog and AD is that the former involves a functional cognitive impairment, often reversible, and manifests as difficulty concentrating, mental slowness, reduced working memory, and sensation (21). However, in AD, cognitive impairment results from progressive neurodegeneration, with loss of synapses and neurons. Symptoms worsen over time and affect episodic memory, language, orientation, and executive functions (22). Brain fog is reversible, has a prevalent synaptic dysfunction, does not accumulate β -amyloid or tau, and presents predominantly with synaptic dysfunction (23).

In AD, abnormal proteins such as β -amyloid plaques accumulate on the outside of neurons and tangles of tau protein inside them. Nerve cells no longer communicate well due to the formation of abnormal neurons that progressively die, especially in the hippocampus. In these atherosclerotic states, neurotransmitter levels, such as acetylcholine, crucial for

memory, decrease (24). As the disease progresses, it spreads to other areas of the CNS, affecting other physiological functions of the brain.

In AD, chronic neuroinflammation in the brain is not just a consequence; it contributes to the progression of the disease. The molecular mechanism of the disease unfolds through the interaction between pathological proteins, brain immune cells, and inflammatory mediators (25).

The deposition of β -amyloid in extracellular plaques and the aggregation of hyperphosphorylated tau protein, which forms intracellular neurofibrillary tangles, are recognized as damage-associated molecular patterns (DAMPs) (26). Additionally, microglia recognize β -amyloid through various receptors, such as Toll-like receptor (TLR)2 and TLR4, TREM2 (crucial for amyloid phagocytosis), CD36, and RAGE (27). Activated microglia induce β -amyloid phagocytosis, reactive oxygen species (ROS) production, and cytokine secretion (28). In this phase, chemokine receptors are also activated, such as CCR1, CCR2, CCR3, CCR5, CXCR1, CXCR2, CXCR3, and CXCR4 (29).

Microglia phagocytose β -amyloid, causing lysosomal damage and oxidative stress, which activate NLRP3, which recruits the ASC protein (30). Caspases are also activated, converting the inactive forms of IL-1 β and IL-18 into the highly inflammatory mature forms (31). Additionally, other pro-inflammatory cytokines such as IL-6 and TNF are also generated, contributing to CNS inflammation (32). The main molecular signalling pathways involved are NF- κ B, which transcribes inflammatory genes, JAK/STAT in response to cytokines, MAPK (p38, JNK) involved in cellular stress, NLRP3 inflammasome in persistent inflammation, increased ROS, and reduced mitochondrial function (33). Inflammation reduces synaptic plasticity, alters neuronal transmission, and causes neuronal death. In this inflammatory network, astrocytes are also activated to produce TNF, IL-6, and nitric oxide (34). Astrocyte activation can lead to brain neurotoxicity and induce synapse loss (35). Furthermore, inflammation promotes tau phosphorylation, which further amplifies the inflammatory response (36).

Brain fog is a functional cognitive disorder, which can also be reversible, that involves difficulty concentrating, confusion, and mental slowness. On the other hand, AD is a chronic, progressive neurodegenerative disease that leads to cognitive impairment, language difficulties, and neuronal loss (37).

CONCLUSIONS

SARS-CoV-2 infection can affect the CNS, with persistent immune activation, neuroinflammation, and alterations in immune cells. CNS involvement is a central aspect of post-COVID-19, with major symptoms including fatigue and brain fog. Brain fog can be caused by stress or fatigue and usually improves when the cause is resolved, whereas AD symptoms progressively worsen over time. In AD, β -amyloid and tau activate microglia, leading to the production of inflammatory molecules that cause synapse loss, neuronal death, and cognitive decline.

Brain fog can appear similar to the early stages of AD, and both conditions share some characteristics, such as microglial activation and NF- κ B activation with the production of inflammatory cytokines, but later they are quite distinct. AD involves accumulation of β -amyloid, hyperphosphorylation of the tau protein, progressive synapse loss, and neuronal death, whereas in brain fog, neurons are largely still present but function less effectively due to inflammation.

Conflict of interest

The authors declare that they have no conflict of interest.

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