

The Cognitive Deficit Induced by Neuroinflammation is Linked to Autonomic Dysfunction in Neurodegenerative Diseases

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Dear Sir,

We wish to draw attention to the intriguing relationship between neuroinflammation, cognitive deficits, and autonomic dysfunction in the context of neurodegenerative diseases.

Neuroinflammation is the condition which refers to inflammation or inflammatory responses in the brain or central nervous system (CNS). The key components of neuroinflammation include microglial activation, astrocyte disruption, cytokines and chemokines overproduction, or damage of the blood brain barrier.

While acute neuroinflammation is a protective response to injury or infection, chronic neuroinflammation can have detrimental effects on brain function. Prolonged activation of glial cells and the release of harmful cytokines and reactive molecules can damage neurons and accelerates neurodegeneration, impairing their ability to repair or to transmit signals properly, with symptoms manifested as cognitive impairment, memory loss and attention deficits.

When inflammatory processes get activated in the brain, plaques accumulate in the synaptic cleft. As a result, various signaling pathways get stimulated causing to activation of neuroglia and astrocytes, the CNS-resident immune cells. This leads to release of many chemokines and cytokines, such as cysteine-X-cysteine Chemokine Receptor type 4 (CXCR4), CXCR7 and CXC ligand 12. The interaction of these chemokines produces loss of neurons and degeneration in areas related to learning.^[1] Lipopolysaccharide (LPS) has been found to activate immune signaling pathways, such as microglia, interleukins, and toll-like receptors, which can further contribute to impairments in cognitive function. Several mechanisms have been studied to be the basis of LPS-induced memory deficits, including neuroinflammation, alterations in synaptic plasticity, disruption of neurotransmitter systems, and dysfunction of the blood-brain barrier.^[2] In addition, several inflammatory markers such as

α -1-Antichymotrypsin, homocysteine, C-reactive protein, interleukin-6, lipoprotein-associated phospholipase A2 activity, and fibrinogen are altered in dementia.^[3-5]

The Central Autonomic Network (CAN) is a network of brain areas that includes structures like the amygdala, hippocampus, anterior cingulate cortex, posterior orbitofrontal cortex, and insula, which are involved in controlling the autonomic nervous system. CAN areas are in connection with brain structures like hypothalamus, periaqueductal grey, parabrachial region, nucleus tractus solitarius, and ventrolateral medulla. Neurodegenerative conditions like multiple system atrophy, PD, and Lewy body dementia are characterized by autonomic dysfunction, where the CAN areas are found to be affected.^[6] In patients with dementia, autonomic dysfunctions (orthostatic hypotension, sweating abnormalities, blood pressure instability) is quite common, and the patients may present symptoms of autonomic dysfunction before the onset of clinical symptoms of dementia.^[7]

Autonomic dysfunctions have been shown to be associated with inflammation in several disease conditions.^[8,9] Therefore, the cognitive deficit induced by neuroinflammation could be linked to autonomic dysfunction in neurocognitive disorders.

Considering these observations, it is plausible that the cognitive deficits observed in neurodegenerative diseases are not solely due to neuroinflammatory neuronal loss but may also be mediated through inflammation-induced autonomic dysfunction. Further exploration into the inflammatory-autonomic-cognitive axis may yield promising insights for early diagnosis and therapeutic interventions in dementia and related disorders.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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