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Cognitive Decline in Pneumonia: A Neglected Consequence

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A growing body of evidence indicate that adverse clinical outcomes in patients with community-acquired pneumonia (CAP) are not confined to the acute phase of the disease but may also occur months or years later (1). Patients with long-term sequelae post-CAP may experience a deterioration of preexisting comorbidities, the development of new medical comorbidities, and decreased life expectancy due to CAP related long-term mortality (2). Dementia and other less severe forms of cognitive decline are increasingly recognized long-terms sequela in patients with CAP. This editorial review the literature linking CAP to cognitive decline, explores potential mechanisms underlying this association, and highlights the need for further research in this area.

Cognitive decline after a hospitalization for CAP can range from mild impairment to severe dementia. Dementia, the most severe form of cognitive decline, is characterized by a deterioration in cognitive abilities, severe enough to impair activities of daily living and independent function. Several studies have evaluated the risk of cognitive decline and dementia in patients with CAP compared to patients without CAP. Six studies included adult patients hospitalized for CAP in the period before the COVID-19 pandemic (3-8). In all studies patients with CAP were at increased risk of developing cognitive impairment or dementia, with CAP patients at 1.5 to 2.5 times increased risk compared to controls. Two of these studies included patients over 18 years of age (6,8) and one included patients over 45 years of age (7), indicating that the risk for cognitive decline is not limited to elderly patients, occurring across all adult age groups following CAP hospitalization. Additional studies have reported an association of cognitive decline and dementia in patients with CAP due to SARS-CoV-2 (9).

The above-mentioned studies have identified certain risk factors that increase the likelihood of cognitive decline after CAP. These include older age, presence of comorbidities, and CAP severity. Patients who experience severe pneumonia, particularly those requiring intensive care unit admission, mechanical ventilation, or who develop sepsis, are more likely to develop long-term cognitive dysfunction. The presence of delirium during the acute phase of CAP is a predictor of long-term cognitive decline. Patients who experience acute sequelae of CAP related the central nervous system, such as mental status changes, confusion, or delirium, may be at increased risk to develop central nervous system related long-term sequelae such as dementia.

Cognitive impairment following CAP can have profound effects on patients and their families. For many patients, the decline in cognitive function represents a loss of independence, requiring increased support for daily activities such as managing medications, finances, and personal care. In more severe cases, patients may require long-term care or assisted living, placing a significant emotional and financial burden on caregivers. CAP-related cognitive decline also complicates medical management. Patients with cognitive impairment may struggle to adhere to treatment regimens or communicate effectively with healthcare providers, leading to an increased risk of hospital readmission and poorer health outcomes.

Optimal neuronal function requires a carefully regulated microenvironment. The central nervous system macrophages or microglia, play a critical role in maintaining an appropriate brain inflammatory tone. The pathogenesis of dementia is likely multifactorial; however, in some patients, dementia may develop due to inflammation outside of the central nervous system promoting neurodegeneration. Systemic cytokines may signal the central nervous system by crossing the blood-brain barrier and activating microglia and astrocytes to release proinflammatory cytokines, resulting in chronic neuroinflammation. Alternative, systemic cytokines can activate the vagus nerve, which releases proinflammatory cytokines and chemokines within the central nervous system. Chronic neuroinflammation is a known driver of neurodegenerative diseases, including Alzheimer's disease (10). Patients with Alzheimer's disease tend to have higher levels of proinflammatory cytokines, cytokine receptors, and other inflammatory markers in the blood. Prolonged exposure to elevated levels of inflammatory markers can disrupt neuronal communication, leading to neuronal death and contributing to cognitive decline over time. During an episode of CAP, some patients develop a dysregulated inflammatory response, characterized by elevated levels of circulating proinflammatory cytokines (2). A link between this dysregulated systemic inflammation in CAP leading to neuroinflammation may explain the observed clinical association between CAP, cognitive decline, and dementia. Further research is needed to elucidate the mechanisms responsible for the association of CAP with long-term outcomes affecting the central nervous system and other organs (11). A better understanding of the pathophysiology of these sequelae may enable the development of preventive and therapeutic interventions.

At the Norton Infectious Diseases Institute, we are investigating the potential role of the gut and lung microbiota in the cognitive decline observed in some patients after an episode of CAP. The communication network among these organs is defined as the gut-lung-brain axis (12-14). The gut and lung microbiomes modulate the activation of immune cells and maintain a physiologic level of immune activation and inflammation that is important for gut, lung, and brain homeostasis (Figure 1 A). We hypothesize that dementia and other manifestations of cognitive decline following CAP may result from CAP-related microbiome dysbiosis, which causes sustained immune activation, systemic inflammation, and neuroinflammation (Figure 1 B).

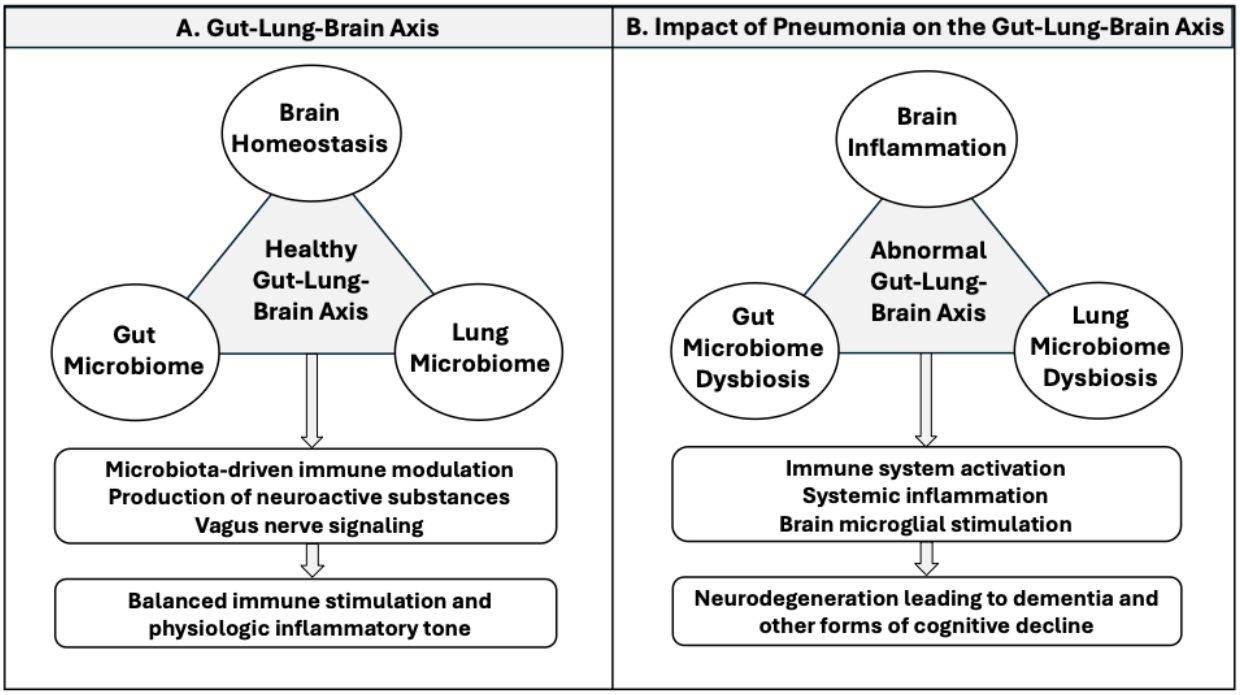

Figure 1: Possible role of the gut-lung-brain axis in the pathogenesis of pneumonia associated cognitive decline.

In conclusion, patients post-CAP have a 1.5 to 2.5 times increased risk of developing dementia compared to populations without CAP. Microglia activation, local production of cytokines, and persistent neuroinflammation likely contribute to the pathogenesis of dementia following CAP. This editorial proposes that CAP-related microbiome dysbiosis, by altering the physiological gut-lung-brain molecular crosstalk, may be responsible for the cognitive decline seen in patients after an episode of CAP.

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