

Treating Chronic Pain in Patients with Comorbid Neurocognitive Disorders

Possible Etiologies of Resistance to Treatment

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Introduction

Over half of individuals with dementia experience chronic pain, contributing to suffering, isolation, and increased healthcare utilization. This effect is not dementia subtype specific, and advanced age further amplifies this effect. Despite high prevalence, management remains inadequate. Current pharmacologic and interventional treatments appear to have limited efficacy. While mechanisms of treatment resistance are unclear, evidence suggests a bidirectional relationship between pain and dementia. This review summarizes current literature and explores proposed pathophysiological mechanisms.

Methods

Non-Systematic Narrative Review. The literature search was conducted using PubMed including papers published prior to March 2024.

Discussion

Dementia and chronic pain intersect biologically and clinically. Impaired self-reporting complicates assessment and treatment while shared mechanisms, including locus coeruleus dysfunction, microglial-driven neuroinflammation, central sensitization, and gray matter changes contribute to persistent pain and cognitive decline. A multimodal management approach appears to be optimal. However, pharmacologic strategies could focus on enhancing descending inhibition and minimizing anticholinergic burden. Emerging glial-targeted therapies show promise, and future work should explore mechanism-based interventions.

Results

Impaired communication in dementia, especially regarding the affective-motivational aspects of pain, compromises physician pain assessment and treatment response monitoring. Neuroimaging demonstrates structural overlap between dementia and chronic pain. Both involve hippocampal and amygdala atrophy and gray matter loss in regions mediating memory, emotion, and pain perception. Pain catastrophizing further correlates with altered connectivity and neuroplastic changes, linking persistent pain to further cognitive decline. Neuroinflammation and microgliosis appear to be central mechanisms driving this relationship. Early microglial activation may promote amyloid clearance but chronic activation drives pro-inflammatory signaling, excitotoxicity, and impaired synaptic regulation. This “inflammaging” process contributes to both central sensitization in pain and progressive neurodegeneration in Alzheimer’s disease. Biomarkers of microglial activation and tau-mediated hippocampal atrophy reinforce this overlap. Furthermore, noradrenergic dysregulation within the locus coeruleus exacerbates both conditions. Loss of norepinephrine impairs microglial function and shifts locus coeruleus function from pain inhibition to facilitation. Cumulatively, these findings underscore shared mechanisms and highlight potential therapeutic targets for addressing pain in dementia.

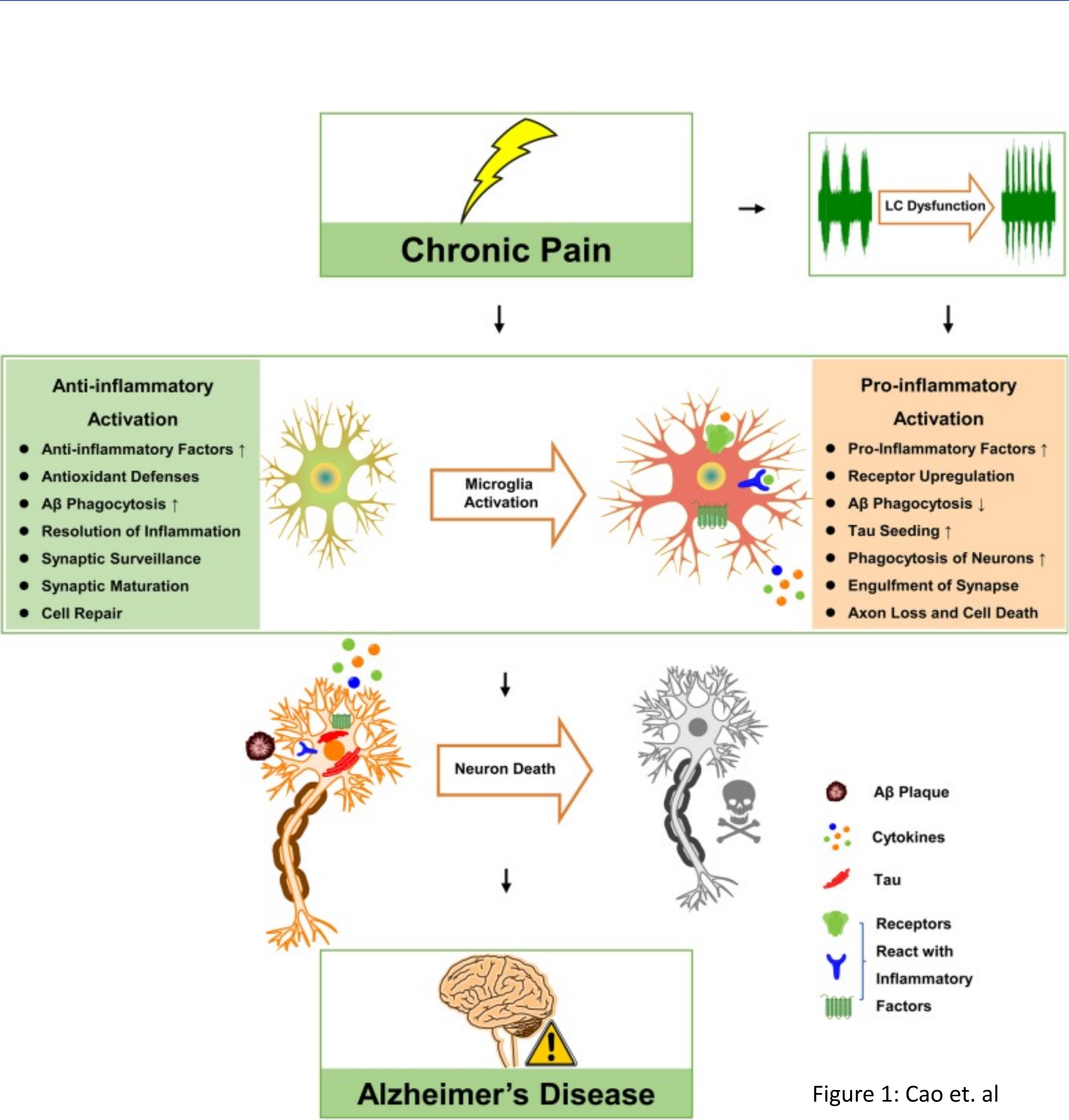


Figure 1: Cao et. al

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