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Editorial

Distant Origins of Local Pathologies: Rethinking the Systemic Roots of Alzheimer's Disease and Beyond

Alzheimer's disease appears to be a neurological condition; however, much of its underlying pathology may originate from distant systems outside the brain. In clinical practice, this disease presents as memory decline accompanied by increasing impairment in daily functioning. Nevertheless, what remains unseen is the prolonged, interdependent communication among the liver, gastrointestinal tract, immune system, vasculature, and brain that contributes to the development of this condition. Recent research encourages reframing Alzheimer's from an isolated cerebral disorder with systemic complications to a systemic illness that ultimately presents with cognitive impairment. This perspective fundamentally changes our approach to identifying risk factors, designing clinical trials, and discussing preventative strategies.[1, 2]

Among the most compelling aspects of this systemic view is the growing evidence for gut–brain crosstalk in Alzheimer's disease. Reviews now detail how gut dysbiosis can sustain chronic low-grade inflammation, generate neuroactive metabolites, and modulate blood–brain barrier integrity and microglial function, thereby shaping the brain's vulnerability long before symptoms appear.[3] In experimental systems and emerging human data, alterations in gut microbial composition are associated with amyloid accumulation, neuroinflammation, and cognitive deterioration. Interventions aimed at modulating the microbiome—such as dietary adjustments, probiotics, or fecal microbiota transplantation—demonstrate preliminary indications of affecting these pathways. Despite robust associations, definitive causal evidence from large-scale randomized human trials is still emerging; current findings derive largely from observational cohorts and preclinical models. For clinical practitioners, this suggests the gut no longer represents mere background biology; it constitutes a potential upstream target where efforts may ultimately decrease the likelihood or rate of neurodegenerative processes.[4, 5]

The liver has assumed a more prominent role in the context of Alzheimer's disease. Hepatic dysfunction, as seen in conditions such as metabolic dysfunction-associated steatotic liver disease or non-alcoholic fatty liver disease (NAFLD/MASLD) and insulin resistance, can impair amyloid-β clearance, disrupt lipid metabolism, and exacerbate systemic inflammatory signaling. Collectively, these effects create a peripheral environment that predisposes the brain to protein accumulation, vascular injury, and synaptic dysfunction. Metabolic syndrome and its hepatic manifestations are thus recast from mere "comorbidities" into active contributors that may prime neural circuits for later failure. This reconceptualization bears significance for clinical practice: by proactively treating metabolic and hepatic diseases during midlife, healthcare providers may not only prevent cirrhosis or myocardial infarction but also mitigate long-term dementia risk, even if current guidelines have yet to fully incorporate this perspective.[2, 6]

A common theme running through these organ-specific narratives is systemic inflammation as a slow, pervasive force connecting peripheral dysfunction to central degeneration. Contemporary reviews of inflammation in Alzheimer's disease underscore that chronic peripheral immune activation, altered cytokine profiles, and age-related modifications in immune cell metabolism are not mere passive reflections of cerebral pathology but active contributors to its onset and progression. Inflammatory mediators have the capacity to weaken vascular and barrier integrity, disrupt glymphatic and lymphatic clearance mechanisms, and maintain microglia in a primed state, wherein modest insults can result in disproportionate damage over time. Vascular endothelial dysfunction and cerebral small-vessel disease provide an additional direct conduit linking systemic inflammation and metabolic stress to cerebral hypoperfusion, blood–brain-barrier breakdown, and white-matter injury—mechanisms increasingly recognized as central drivers of Alzheimer's progression. For patients, this implies recognizing that

cardiovascular risk factors, chronic infections, autoimmune disorders, and lifestyle behaviors that perpetuate systemic inflammation are integral to their cognitive health trajectory, rather than unrelated issues to be addressed separately in clinical practice.[7, 8]

Most importantly, Alzheimer's disease is not the sole condition exhibiting the pattern of "distant origins, local pathology." Broader research into neurodegenerative disorders emphasizes common motifs such as peripheral immune cell involvement, systemic metabolic disturbances, and organ–brain interactions observed in Parkinson's disease, amyotrophic lateral sclerosis, and related illnesses. The debate now centers not on whether peripheral systems communicate with the brain, but rather on its timing, persistence, and the predominant channels involved in each disease. Evidence addressing the "systemic implications" of Alzheimer's disease currently contends that muscular, hepatic, vascular, and immune manifestations are fundamental to its biology rather than incidental, thereby encouraging a holistic approach in teaching and practicing neurology that considers the entire organism.[7, 9]

If we accept distant origins shape local pathologies, several commitments follow for researchers and clinicians. Longitudinal Alzheimer's cohorts should routinely integrate measures of liver function, metabolic health, inflammatory status, and gut microbial features with imaging and cognitive data, employing multi-omics strategies to identify systemic signatures that precede overt dementia by years. Therapeutic development must move beyond the notion that amyloid- or tau-targeted agents can, in isolation, reverse a brain embroiled in chronic metabolic and inflammatory stress, and instead complement these central approaches with rational combinations that enhance systemic health and modulate the microbiome. Perhaps most crucially, the discourse provided to patients and trainees must evolve: Alzheimer's disease should be understood not as an abrupt, late-life cerebral failure, but as a long-term systems disorder in which the liver, gut, immune system, vasculature, and brain co-evolve over decades. "Distant origins of local pathologies" challenges us to follow the disease upstream, to intervene earlier and more comprehensively, and to regard every organ currently under treatment as part of the brain we aim to protect in the future.[2, 5, 6, 10]

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