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Alzheimer's disease: new perspectives-a review of emerging evidence-based concepts and therapeutics

Abstract

In this review, I evaluate emerging evidence regarding the etiology and treatment of Alzheimer's disease (AD), focusing on the limitations of the amyloid hypothesis and proposing a shift toward a framework centered on cholinergic failure. I argue that this failure results from an *inflammation-induced cascade* contributed to by infectious exposures (specifically HSV and VZV), potential toxic exposures exacerbated by genetic predisposition, and various lifestyle factors. Utilizing RNA-seq analysis of datasets from the Gene Expression Omnibus and ethically sourced liver tissue, I assess detoxification gene expression and its role in managing environmental stressors. I contend that the convergence of these factors culminates in a failure to maintain adequate levels of Nerve Growth Factor (NGF), resulting in the loss of viability of cholinergic nerves in the brain. Furthermore, I discuss risk assessment and stratification and provide options for risk management through targeted interventions. I prioritize cholinergic intervention and infectious control, followed by lifestyle and detoxification considerations, and discuss the potential of acetylcholinesterase inhibitors (AChEIs) in supporting neuronal survival.

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Introduction

The historical dominance of the amyloid hypothesis has guided drug development for decades with meager clinical results.[1] While anti-amyloid monoclonal antibodies are now available and may offer some utility in slowing plaque accumulation, their clinical benefits remain limited.[2] These therapies are also associated with considerable toxicity, including amyloid-related imaging abnormalities (ARIA) and, in rare instances, death.[3]

In this paper, I propose that structural deterioration of the AD brain is primarily a cholinergic failure resulting from a chronic, multi-factorial inflammatory cascade.[4,5] This cascade is fueled by a synergy of infectious agents and potential toxic exposures, made worse by an individual's genetic predisposition and various lifestyle factors. I hypothesize that the cumulative effect of these stressors leads to a critical biological threshold: the failure to maintain adequate levels of Nerve Growth Factor (NGF). Without sufficient NGF support, cholinergic neurons lose viability, leading to the cognitive and structural decline characteristic of AD.

Methods

Literature selection

I conducted a systematic search via PubMed, focusing on peer-reviewed primary research, meta-analyses, and clinical trials (1990–2025).

Transcriptomic analysis and statistical rigor

To investigate the role of detoxification as a contributor to the inflammatory cascade, I utilized gene set expression analysis with transcriptomic data from the Gene Expression Omnibus (GEO). I also organized an RNA-seq gene set expression analysis of ethically sourced liver tissue in a commercial, accredited research lab.[6]

Gene Selection: I utilized a set of 203 genes known to be active in detoxification pathways. This gene set was curated from CYP450, UGT, and other known detoxification gene families; peer reviewed/reported gene sets; and individually identified genes from a spectrum of peer reviewed papers. This mix of objectively and subjectively selected genes was intended to be specifically focused on detoxification relevant genes, without the more inclusive gene ontology sets more appropriate for gene set *enrichment* studies. Full details of this process are reported in the full manuscript documenting that evaluation.[6]

GEO Data set selection: I searched the GEO data repository using the search terms: Alzheimer's, human, RNA-seq, and GEO2R (a GEO associated analytic tool.) I identified over 90 data sets. I then scrutinized the metadata groupings, statistical methods, and data pertinent to the detoxification gene project, analyzing the peer reviewed papers from which those data sets were derived. I found 8 pertinent data sets. The data set selection process has objective features but also is unavoidably subjective.

Statistical methods: Differentially expressed genes (DEGs) were identified in analyses of various iterations of each data set, noting statistical significance of detoxification genes using adjusted p-values of < 0.05, and to ensure the highest degree of statistical significance.[7]

Liver tissue process: To define detoxification dynamics in non-brain tissues from AD subjects, I located such AD tissue and otherwise similar control samples from Russian subjects through a certified biobank. A commercial genomics lab processed the tissue and carried out RNA-seq, organizing and reporting the data from this part of the study. Statistical significance was based on q-values of < 0.05 which, though similar to adjusted p-value, control for false discovery rate.[8]

Statistical visualization: In the referenced full report of the transcriptomic study, graphical visualization of dispersion estimates, UMAP plots, scatter plots, and volcano plots are provided for each of the analyzed GEO data sets.

Fold change comparisons are utilized to indicate whether expression changes indicate over-expression (positive number) or under-expression (negative number.)

Results

The Cholinergic-NGF axis

My review of the literature suggests that the central etiology of AD is likely to be an inflammation-associated deterioration of cholinergic

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neurons due to a lack of trophic support. The inability to maintain Nerve Growth Factor (NGF) levels appears to be the terminal event in the inflammatory cascade, leading directly to the loss of neuronal viability.[9,10]

Infectious and toxic contributions

Infectious Synergy (HSV-1): I prioritize the role of Herpes Simplex Virus (HSV-1) as a central infectious driver. Evidence for its role includes the presence of HSV-1 DNA within amyloid plaques and epidemiological data showing that anti-herpetic treatments potentially reduce AD risk in infected populations.[11–15] VZV often stimulates reactivation of HSV-1, triggering latent HSV in the brain.[16] Notably, VZV also possesses its own primary brain inflammation-inducing features, contributing independently to the neuroinflammatory burden.

Detoxification Deficiency: RNA-seq analysis of GEO datasets and bio-banked liver tissue reveal significant changes in expression, both up and down, in detoxification genes.[6] These fluctuations suggest a systemic dysregulation in clearing metabolic and environmental stressors, which exacerbates the neuroinflammatory state.[17,18]

The role of APOE and the cysteine-glutathione axis

The APOE gene isoforms (APOE2, 3, and 4) exhibit critical structural differences defined by their cysteine content. APOE2 contains two cysteine residues, APOE3 contains one, and APOE4 contains none.[19] These structural variations have profound implications for antioxidant defense; cysteine is a rate-limiting precursor for the synthesis of glutathione, the brain's primary endogenous antioxidant.[20,21]

Glutathione plays a vital role in protecting neurons from oxidative stress, free radical damage, and infectious insults. Because APOE4 lacks these cysteine residues, individuals carrying this allele may have a diminished capacity to maintain robust glutathione levels. This deficiency leaves the brain significantly more vulnerable to the inflammatory cascade, as the lack of cysteine-mediated protection limits the ability to neutralize the oxidative and infectious problems that ultimately deplete NGF and compromise cholinergic nerve viability.[22,23]

Discussion

Risk assessment, stratification, and management

I propose that clinical focus shift toward a tiered framework for risk assessment:

1. Genetic/Lifestyle Markers: Assessment of APOE status (specifically the cysteine-glutathione axis) alongside lifestyle factors such as chronic sleep deprivation, sedentary behavior, and high-glycemic diets that drive systemic inflammation.
2. Infectious Load: Serology and clinical history of HSV-1 and VZV reactivation.
3. Metabolic/Toxic Capacity: Assessing systemic detoxification issues, considering limitation of toxic exposures and/or use of bile acid sequestration[24] in selected individuals, particularly in the context of appropriately designed clinical trials as or if they become available.

Risk management should prioritize cholinergic intervention, followed by infectious control, and lower in the order of importance but still potentially significant, lifestyle and detoxification considerations.

Prophylaxis of neurodegeneration and Off-label utility

I argue that we can safely, carefully, and ethically employ off-label use of certain drugs that are already FDA-approved for other purposes to prophylax neurodegeneration.[25]

- **Bile Acid Sequestrants:** Traditionally used for cholesterol management, these may be repurposed to reduce the toxic inflammatory load that may add to depletion of NGF.[26–28]
- **AChEIs:** While approved for symptomatic AD, their earlier use may support the cholinergic network before terminal atrophy occurs.[29–31]

This strategy offers a lower-risk profile compared to current anti-amyloid therapies. While anti-amyloid drugs may have a niche role, their limited benefit and potential for toxicity make them less desirable than repurposing established, safer compounds that target the inflammatory and trophic origins of the disease.

Conclusion

I propose a unifying framework where Alzheimer's Disease is viewed not as a primary amyloid-driven neurodegenerative process, but as the final stage of a *cholinergic failure* induced by a chronic, multi-systemic inflammatory cascade. The shift from an amyloid-centric model to a trophic-support model recognizes that the accumulation of beta-amyloid is likely a reactive marker of damage rather than the engine of the disease itself. By the time amyloid plaques are visible, the underlying neuroinflammatory drivers-infectious pathogens, toxic stressors, and genetic vulnerabilities—have likely been active for decades.[32]

Central to this new perspective is the *failure to maintain adequate Nerve Growth Factor (NGF) levels,* which serves as the critical juncture between systemic inflammation and structural brain deterioration. When glutathione-dependent defenses fail-as they are prone to do in the absence of APOE-mediated cysteine support-the brain enters a state of persistent oxidative and infectious vulnerability. In this environment, pathogens like HSV-1 and VZV trigger a cytokine-driven cascade that depletes NGF, stripping cholinergic neurons of the trophic support required for their viability.[33,34]

We must pivot away from high-cost, high-toxicity anti-amyloid therapies that offer limited clinical returns and a notable risk of death. Instead, we should prioritize the *safe, off-label use of established FDA-approved medications* that can be deployed immediately within an evidence-based framework. Interventions such as early cholinergic support with AChEIs, aggressive infectious control, and, potentially, systemic detoxification via bile acid sequestration represent a more resource-efficient and physiologically sound path toward prophylaxis.

By integrating transcriptomic insights with personalized risk stratification, we can identify and intervene in the inflammatory process long before it culminates in irreversible cholinergic atrophy. The preservation of the cholinergic-NGF axis represents the most promising therapeutic target for the coming decade, offering a strategy that focuses on maintaining neuronal life rather than simply managing the detritus of neuronal death.

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Conflicts of interest

The author declares that there are no conflicts of interest.

References

1. Kepp KP. The amyloid cascade hypothesis: an updated critical review. *Brain*. 2023;146(10):3969–3990.
2. Høilund-Carlsen PF, Alavi A, Castellani RJ, et al. Alzheimer's amyloid hypothesis and antibody therapy: melting glaciers? *Int J Mol Sci.* 2024;25(7):3892.
3. Piller C. Brain games? *Science*. 2023;382(6672):754–759.
4. Ferreira-Vieira TH, Guimarães IM, Silva FR, et al. Alzheimer's disease: targeting the cholinergic system. *Curr Neuropharmacol*. 2016;14(1):101–115.
5. Hampel H, Mesulam MM, Cuello AC, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain.* 2018;141(7):1917–1933.
6. McCaulley ME. Impaired pathways of detoxification and risk of Alzheimer's disease in humans-differential gene expression studies via gene set expression analysis. medRxiv. Preprint posted May 29, 2025.
7. Jafari M, Ansari-Pour N. Why, when and how to adjust your P values? *Cell J.* 2019;20(4):604–607.
8. Lai Y. A statistical method for the conservative adjustment of false discovery rate (q-value). *BMC Bioinformatics.* 2017;18(Suppl 3):69.
9. Moss DE. *Alzheimer's: My Journey to a Next Generation Treatment*. Menlo Park, CA: Bear Run Publisher; 2013.
10. Moss DE, Perez RG. The phospho-tau cascade, basal forebrain neurodegeneration, and dementia in Alzheimer's disease: anti-neurodegenerative benefits of acetylcholinesterase inhibitors. *J Alzheimers Dis.* 2024;102(3):617–626.
11. Fraser NW, Lawrence WC, Wroblewska Z, et al. Herpes simplex type 1 DNA in human brain tissue. *Proc Natl Acad Sci U S A*. 1981;78(10):6461–6465.
12. Jamieson GA, Maitland NJ, Wilcock GK, et al. Latent herpes simplex virus type 1 in normal and Alzheimer's disease brains. *J Med Virol*. 1991;33(4):224–227.
13. Vestin E, Boström G, Olsson J, et al. Herpes simplex viral infection doubles the risk of dementia in a contemporary cohort of older adults: a prospective study. *J Alzheimers Dis.* 2024;97(4):1841–1850.
14. Feng H, Pan K, Shabani ZI, et al. Association between herpesviruses and Alzheimer's disease: a meta-analysis based on case-control studies. *Mol Cell Biochem.* 2025;480(7):4079–4090.
15. Weidung B, Hemmingsson ES, Olsson J, et al. VALZ-Pilot: high-dose valacyclovir treatment in patients with early-stage Alzheimer's disease. *Alzheimers Dement (N Y)*. 2022;8(1):e12264.
16. Cairns DM, Itzhaki RF, Kaplan DL. Potential involvement of varicella zoster virus in Alzheimer's disease via reactivation of quiescent herpes simplex virus type 1. *J Alzheimers Dis.* 2022;88(3):1189–1200.
17. Vasefi M, Ghaboolian-Zare E, Abedelwahab H, et al. Environmental toxins and Alzheimer's disease progression. *Neurochem Int.* 2020;141:104852.
18. Dhapola R, Sharma P, Kumari S, et al. Environmental toxins and Alzheimer's disease: a comprehensive analysis of pathogenic mechanisms and therapeutic modulation. *Mol Neurobiol.* 2024;61(6):3657–3677.
19. Fernández-Calle R, Konings SC, Frontiñán-Rubio J, et al. APOE in the bullseye of neurodegenerative diseases: impact of the APOE genotype in Alzheimer's disease pathology and brain diseases. *Mol Neurodegener.* 2022;17:62.
20. Dröge W, Breitkreutz R. Glutathione and immune function. *Proc Nutr Soc*. 2000;59(4):595–600.
21. Pastore A, Federici G, Bertini E, et al. Analysis of glutathione: implication in redox and detoxification. *Clin Chim Acta.* 2003;333(1):19–39.
22. Burgos JS, Ramirez C, Sastre I, et al. Effect of apolipoprotein E on the cerebral load of latent herpes simplex virus type 1 DNA. *J Virol.* 2006;80(11):5383–5387.
23. Chen F, Ke Q, Wei W, et al. Apolipoprotein E and viral infection: risks and mechanisms. *Mol Ther Nucleic Acids.* 2023;33:529–542.
24. Huang F, Pariante CM, Borsini A. From dried bear bile to molecular investigation: a systematic review of the effect of bile acids on cell apoptosis, oxidative stress and inflammation in the brain across preclinical models. *Brain Behav Immun.* 2022;99:132–146.
25. Furey K, Wilkins K. Prescribing "off-label": what should a physician disclose? *AMA J Ethics.* 2016;18:587–593.
26. Feng Y, Li Q, Ou G, et al. Bile acid sequestrants: a review of mechanism and design. *J Pharm Pharmacol*. 2021;73(7):855–861.
27. Ast M, Frishman WH. Bile acid sequestrants. *J Clin Pharmacol.* 1990;30(2):99–106.
28. Møller JJ, Lyngberg AC, Hammer PEC, et al. Substantial decrease of PFAS with anion exchange resin treatment: a clinical cross-over trial. *Environ Int.* 2024;185:108497.
29. Dubois B, Chupin M, Hampel H, et al. Donepezil decreases annual rate of hippocampal atrophy in suspected prodromal Alzheimer's disease. *Alzheimers Dement.* 2015;11(9):1041–1049.
30. Cavedo E, Grothe MJ, Colliot O, et al. Reduced basal forebrain atrophy progression in a randomized donepezil trial in prodromal Alzheimer's disease. *Sci Rep*. 2017;7(1):11706.
31. Krishnan KR, Charles HC, Doraiswamy PM, et al. Randomized, placebo-controlled trial of the effects of donepezil on neuronal markers and hippocampal volumes in Alzheimer's disease. *Am J Psychiatry.* 2003;160(11):2003–2011.
32. Rafii MS, Aisen PS. Detection and treatment of Alzheimer's disease in its preclinical stage. *Nat Aging*. 2023;3(5):520–531.
33. Cuello AC, Pentz R, Hall H. The brain NGF metabolic pathway in health and in Alzheimer's pathology. *Front Neurosci.* 2019;13:62.
34. Cuello AC, Bruno MA, Allard S, et al. Cholinergic involvement in Alzheimer's disease: a link with NGF maturation and degradation. *J Mol Neurosci*. 2010;40(1-2):230–235.

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