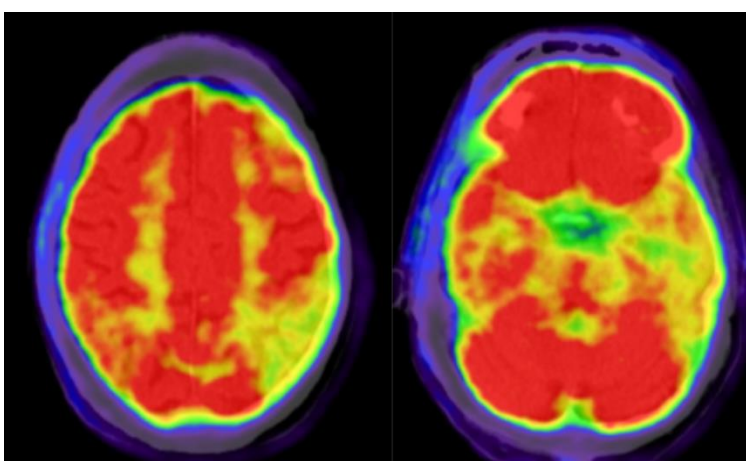
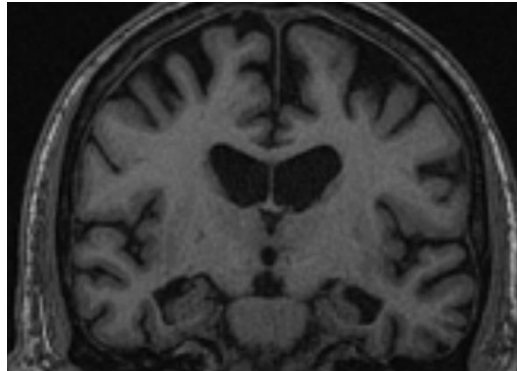


Iron Overload, Hypothyroidism, and Alzheimer’s Disease: A Synergistic Effect Hypothesis

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OBJECTIVE				
To describe a case of early-onset Alzheimer’s disease (EOAD) arising in a patient with concurrent hereditary hemochromatosis (HFE) and central hypothyroidism, and to propose a synergistic (“double-hit”) mechanism linking iron and thyroid dyshomeostasis to accelerated neurodegeneration.				
BACKGROUND	METHODS	DISCUSSION	DISCUSSION	REFERENCES
Iron is an essential transition metal central to mitochondrial and microglial function, neurotransmitter synthesis, and synaptic plasticity. Thyroid hormones (TH) are equally critical to brain metabolism and mitochondrial activity. Both iron overload and hypothyroidism-induced oxidative stress can result in microglial dysfunction and causes a pro-inflammatory M1 state, which may induce ferroptosis and neuronal cell death, and represent pathways of interest in neurodegeneration.	Male • Onset ~age 64 • 5-year progressive word-finding difficulties and short-term memory loss Language-predominant cognitive decline FDG-PET Hypometabolism L > R parietotemporal AD-pattern topology Amyloid PET Positive Amyloid pathology confirmed ApoE Genotype • ε3/ε3 No ε4 allele Standard genetic risk Thyroid Function Central hypothyroidism ↓ free T4 • ↓ TSH Ferritin ~900s ng/mL Hereditary hemochromatosis • HFE homozygous Managed with phlebotomy Iron overload comorbidity Diagnosis Biomarker-confirmed Logopenic Variant Primary Progressive Aphasia (lvPPA) Alzheimer’s pathology	CENTRAL HYPOTHYROIDISM + IRON OVERLOAD Low fT4 / low TSH Hemochromatosis • ferritin ~900s ↑ Oxidative stress • impaired ROS clearance M1 microglial activation & neuroinflammation Ferroptosis • ↑ Amyloid-β • ↑ Tau phosphorylation Hippocampal apoptosis & ↓ brain resilience Accelerated early-onset Alzheimer’s disease	➤ Intracellular free iron lead to mitochondrial injury, ROS and lipid peroxidation ➤ The dual effect of iron dyshomeostasis and thyroid dysfunction may exert a synergistic or additive effect in ferroptosis and decreased brain resilience leading to earlier AD clinical onset.	1. Kim DK, Choi H, Lee W, et al. Brain hypothyroidism silences the immune response of microglia in Alzheimer’s disease animal model. <i>Sci Adv.</i> 2024 2. AlAnazi FH, Al-Kuraishy HM, Alexiou A, et al. Primary Hypothyroidism and Alzheimer’s Disease: A Tale of Two. <i>Cell Mol Neurobiol.</i> 2023 3. Mezzanotte M, Stanga S. Brain Iron Dyshomeostasis and Ferroptosis in Alzheimer’s Disease Pathophysiology: Two Faces of the Same Coin. <i>Aging Dis.</i> 2024. 4. Wang F, Wang J, Shen Y, Li H, Rausch WD, Huang X. Iron Dyshomeostasis and Ferroptosis: A New Alzheimer’s Disease Hypothesis?. <i>Front Aging Neurosci.</i> 2022 5. Tran D, DiGiacomo P, Born DE, Georgiadis M, Zeineh M. Iron and Alzheimer’s Disease: From Pathology to Imaging. <i>Front Hum Neurosci.</i> 2022;16:838692. Published 2022 Jul 13. 6. Köhrle J. Selenium, Iodine and Iron-Essential Trace Elements for Thyroid Hormone Synthesis and Metabolism. <i>Int J Mol Sci.</i> 2023 7. Atkins JL, Pilling LC, Heales CJ, et al. Hemochromatosis Mutations, Brain Iron Imaging, and Dementia in the UK Biobank Cohort. <i>J Alzheimers Dis.</i> 2021 8. Garofalo V, Condorelli RA, Cannarella R, Aversa A, Calogero AE, La Vignera S. Relationship between Iron Deficiency and Thyroid Function: A Systematic Review and Meta-Analysis. <i>Nutrients.</i> 2023 9. Zhu Z, Li J, Peng Y, et al. Multi-metal mixture exposure and cognitive function in urban older adults: The mediation effects of thyroid hormones. <i>Ecotoxicol Environ Saf.</i> 2025
METHODS	➤ HFE common genetic mutations have been found associated with increased risk for dementia in homozygote’s men and increased iron accumulation including in hippocampi ➤ Iron accumulation can cause significant endocrine disruption via the pituitary-hypothalamic axis ➤ Iron is also an essential cofactor for TH synthesis via the thyroperoxidase enzyme			
 Figure 1: FDG-PET scan showing the predominant left parietotemporal hypometabolism  Figure 2: MRI brain, T1 Coronal view showing asymmetric atrophy more prominent on left, particularly in the perisylvian/posterior temporal region and cortical thinning	➤ Recent murine studies show TH deficiency causes spontaneous microglial activation and resulting in impaired immune response to inflammatory stimuli or amyloid, worsening AD pathology. ➤ Hypothyroidism may limit ROS clearance, increase amyloid-β deposition and tau phosphorylation, and contribute to hippocampal apoptosis, neuroinflammation, and neurodegeneration			
CONCLUSION			Iron and TH dyshomeostasis may produce a “double-hit” phenomenon that accelerates neurodegeneration via microglial dysfunction. Co-existing iron overload and central hypothyroidism may lower patient’s threshold for AD pathology, contributing to early onset In EOAD presenting without an ε4 allele or family history, clinicians should evaluate for modifiable metabolic contributors — including thyroid function and iron studies (ferritin) — as potential disease modifiers	
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