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Getting the iron out: Phlebotomy for Alzheimer's disease?

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SUMMARY

This communication explores the temporal link between the age-associated increase in body iron stores and the age-related incidence of Alzheimer's disease (AD), the most prevalent cause of senile dementia. Body iron stores that increase with age could be pivotal to AD pathogenesis and progression. Increased stored iron is associated with common medical conditions such as diabetes and vascular disease that increase risk for development of AD. Increased stored iron could also promote oxidative stress/free radical damage in vulnerable neurons, a critical early change in AD. A ferrocentric model of AD described here forms the basis of a rational, easily testable experimental therapeutic approach for AD, which if successful, would be both widely applicable and inexpensive. Clinical studies have shown that calibrated phlebotomy is an effective way to reduce stored iron safely and predictably without causing anemia. We hypothesize that reducing stored iron by calibrated phlebotomy to avoid iron deficiency will improve cerebrovascular function, slow neurodegenerative change, and improve cognitive and behavioral functions in AD. The hypothesis is eminently testable as iron reduction therapy is useful for chronic diseases associated with iron excess such as nonalcoholic steatohepatitis (NASH), atherosclerosis, hereditary hemochromatosis and thalassemia. Testing this hypothesis could provide valuable insight into the causation of AD and suggest novel preventive and treatment strategies.

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Introduction

AD is a progressive and invariably fatal neurodegenerative disease. By recent estimates, the $100 billion annual cost of providing care for the 4.5 million Americans with AD is expected to rise as the American population ages and prevalence of AD-related risk factors such as adiposity, hyperinsulinemia, and type 2 diabetes mellitus (T2DM) continue to increase [1]. Sporadic, late onset AD comprising the great majority of AD cases, most likely results from the interactions of numerous genetic and environmental factors. Individuals diagnosed with AD survive an average of 5–10 years. During this period, they become increasingly and severely incapacitated. There is no cure for AD. Present pharmaceutical interventions are palliative and marginally effective. New therapies for AD should ideally minimize the impact of coexistent risk factors, and target the earliest and most basic pathophysiological changes in AD when intervention would likely provide the greatest benefit. Further, any intervention should be minimally toxic since long-term treatment will likely be necessary. Advances in brain imaging technologies offer much hope for early diagnosis of AD, but incomplete understanding of AD etiology and pathogenesis has hindered development of effective therapies. An explanatory model of AD etiology and pathogenesis should reconcile risk factors identified from epidemiological studies, the histopathological changes characteristic of AD, and age-related onset and the inexorable progression of the disease. A ferrocentric model of AD development (Fig. 1) aims to achieve this goal.

Multiple studies associate disturbances in metal ion homeostasis with AD and suggest a pathogenic role [2]. Iron is the most abundant redox active metal in humans. Dietary iron is actively absorbed but minimally excreted [3], and there is mounting evidence that body iron stores present in free-living apparently healthy adults, rise with age reaching toxic levels [4–10]. Sullivan [6] raised two important questions in relation to iron and heart disease: first, are body iron stores excessive, even if they fall within clinically "normal" limits? Second, is stored iron safe? We believe

Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; Fpn1, ferroportin; HH, hereditary hemochromatosis; IRE, iron responsive element; IRP, iron regulatory protein; LIP, labile iron pool; T2DM, type 2 diabetes mellitus.

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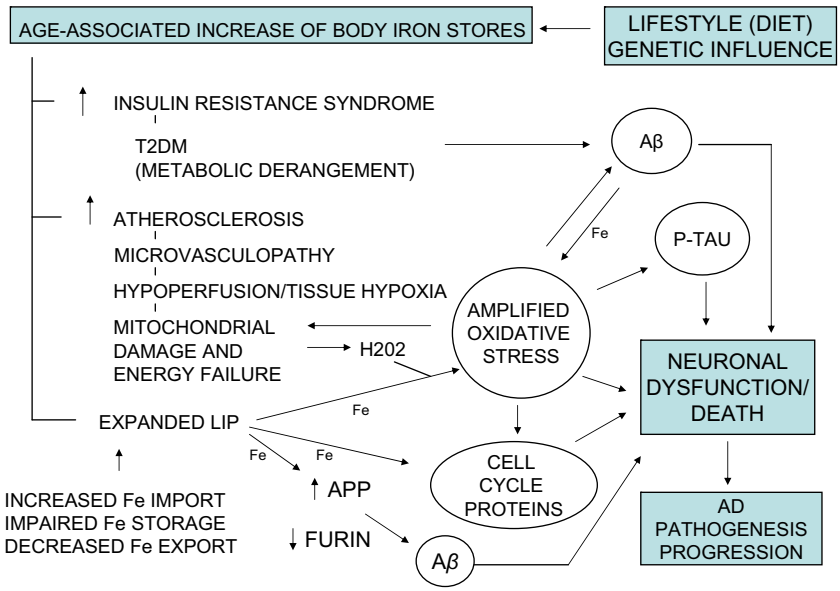

Fig. 1. The pervasive and modifiable role of iron on the development of AD. The most widely accepted theories of AD causation implicate four significant changes: (1) Aβ accumulation, (2) tau hyperphosphorylation and development of neurofibrillary pathology, (3) oxidative stress and free radical damage in vulnerable neurons, and (4) expression of cell cycle proteins in post-mitotic neurons. Age-related increase in stored iron is at the apex of a pathophysiological cascade that could promote these critical changes by increasing the risk for diabetes and cardiovascular disease, two common medical conditions associated with increased risk for AD, and by expanding the pool of redox active iron (LIP) in brain cells. Insulin resistance syndrome and T2DM could increase Aβ accumulation because hyperinsulinemia modifies Aβ metabolism and glycation reactions alter Aβ aggregation [1,28]. Cardiovascular disease causing cerebral hypoperfusion and tissue hypoxia could be a cause of mitochondrial damage and dysfunction that results in increased generation of reactive oxygen species including hydrogen peroxide [45,50]. Increased redox active iron due to increased iron availability and impaired iron storage/detoxification could exacerbate Fenton reaction-mediated oxidative stress and free radical damage to essential cell components. Moreover, mitochondria are both a source of reactive oxygen species and a target of reactive oxygen-mediated oxidative stress, so a vicious circle could develop leading to increased mitochondrial damage and dysfunction. Iron-mediated oxidative stress, perhaps in association with cell signaling disturbances, could promote increased phosphorylation of microtubule-associated protein tau and expression of cell cycle proteins in post-mitotic neurons [91–94]. The figure also depicts a novel pathway by which iron could potentially regulate Aβ accumulation. Expression of furin, a subtilisin-like proprotein convertase that stimulates α-secretase activity, is decreased in AD brain, and brain from Tg2576 AD-transgenic mice [95]. Silvestri and Camaschella [96] proposed that iron-mediated decrease of furin protein and α-secretase activity in AD brain, and iron-mediated increase in APP expression [97], could favor the accumulation of Aβ. The figure does not presume to be an exhaustive review of how AD-related pathology develops, and indeed, does not depict other potentially important developments such as neuroinflammation. Our intent is to highlight potential linkage between increased body iron stores and some potentially important pathophysiological changes in AD that would possibly respond to iron reduction by calibrated phlebotomy.

these questions are relevant to AD whose risk increases with age [11].

Body iron stores increase with age and precede development of AD

Body iron stores increase with age in both men and women. Serum ferritin, which is a useful marker of body iron stores [12], increases sharply between the teenage years and age 40 in men [4,7]. A comparable increase in serum ferritin occurs in women after menopause, between 40–49 and 60–69 years of age. Sullivan recognized that the risk of heart disease in men and women paralleled the increases in body iron stores. He formulated the iron hypothesis of coronary artery disease, which suggests that premenopausal women are protected from atherosclerosis and atherosclerotic events because of low body iron stores until menopause after which body iron stores rise [4–6]. Iron is implicated in the pathogenesis of atherosclerosis, which begins relatively early in life and involves oxidation of low-density lipoprotein by incompletely understood mechanisms [9]. Significantly, the relationship between increased body iron stores and risk of heart disease is observed in men under 50 [13]. AD is a disease of aging; its incidence rises dramatically after 60 years of age [11]. However, changes in brain metabolism can precede disease-associated cognitive decline by decades [14]. Thus, it is likely that an age-associated increase in body iron stores will precede or overlap the early cerebral metabolic changes that presage AD in the majority of elderly individuals eventually diagnosed with this disease.

Cardiovascular disease and diabetes are associated with increased body iron stores and AD risk

AD shares common risk factors with vascular dementia including aging, atherosclerosis, stroke, and type 2 diabetes mellitus (T2DM) [15–18]. Vasculopathy, cerebral hypoperfusion, and tissue hypoxia biologically link these risk factors, and are implicated in the etiology of AD [19,20]. Moreover, these common risk factors for AD are associated with increased body iron stores. Thus, atherosclerosis is associated with increased risk for AD [18,21], and age-associated increase in stored iron is associated with atherosclerosis and vascular disease (discussed in [9]). Stroke increases risk for AD [18], and increased stored iron is associated with poor outcome in stroke [22], possibly due to iron-dependent hypoxia-reperfusion injury. T2DM increases risk for AD and for mild cognitive impairment (MCI), the transitional stage between normal cognition and AD [1,23], and increased stored iron is associated with risk for T2DM [24–27]. T2DM is a complex metabolic disease-associated with obesity, insulin resistance, hypo- and hyperglycemia, atherosclerosis and microvascular disease, and cognitive dysfunction [1]. Insulin resistance syndrome (IRS) (metabolic syndrome) could be an important link between T2DM and risk for AD [1,28]. IRS is a cluster of medical conditions that includes chronically elevated levels of insulin, reduced insulin activity, hyperlipidemia, and cardiovascular effects such as hypertension and atherosclerotic heart disease [29], and the incidence of IRS in both men and women is associated with increased body iron stores [30]. Genetic influences could also be an important link between increased stored iron and AD. Hereditary hemochromatosis (HH) is an autosomal recessive