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Iron Accumulation and Neurodegeneration in Patients with Alzheimer's Diseases: An Integrative Review Study of the Evidence

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Abstract

Iron is essential for virtually all types of cells and organisms. Increased brain iron levels may be a risk factor for age-related neurologic disorders, such as Alzheimer's Disease. In contrast, iron deficiency is the most prevalent nutritional concern worldwide, with many associated cognitive and neural ramifications. Objective: An update, based on current literature, about the iron´s effects on brain homeostasis, as well as its contribution to the pathogenesis of Alzheimer's Disease. Methods: A literature search up to May 2017, repeated in June 2017, was conducted, including clinical trials, preclinical basic research studies, and reviews studies. Conclusion: Increased iron concentration in the cortical and subcortical areas is associated with decreased tissue integrity in patients with Alzheimer's Disease. Histologic and magnetic resonance imaging data, in association with cognitive tasks, have suggested an increase in iron levels in the gray matter in Alzheimer's Disease. Iron deposition in Alzheimer's Disease and the brain lesions may be related to low and long-grade neuroinflammation.

Keywords: *Iron Accumulation; Brain Neurodegeneration; Alzheimer's Disease*

Introduction

Iron is one of the most abundant metals in the human body. It is a trace metal involved in many important biological processes, existing in either ferrous (Fe^{2+}) and ferric (Fe^{3+}) states [1,2]. Oxygen and electron transport; cell proliferation and differentiation; regulation of gene expressions, and DNA, RNA and protein´s synthesis are examples of iron crucial vital roles [3]. Delicate regulation of iron metabolism is relevant for maintaining good health as iron deficiency or its overload can lead to diseases [1]. Iron accumulates progressively in the brain with age; however, the cause is unknown. We hypothesized that iron accumulation may be associated with the age-induced changes in the expression of iron metabolism proteins in the brain. Abnormalities in brain iron metabolism with excessive iron levels give rise to

a variety of neurodegenerative diseases. In recent years, advances in neuroscience, such as cerebral mapping, have led to the identification of several areas that are associated with disturbed iron metabolism and may cause the syndromes of Neurodegeneration with Brain Iron Accumulation (NBIA). These syndromes present clinically with a progressive hypo- and/or hyperkinetic movement disorder and, pathologically, with excessive iron deposition in the brain, particularly affecting the basal ganglia, mainly the globus pallidus (GP) [4-6].

Iron homeostasis is fundamental for normal brain function [4]. Any dysregulation of the above-mentioned iron homeostatic mechanisms may lead to iron depletion or accumulation, which has been proven to be harmful to in vitro neurons. It is already known that iron accumulates with brain aging and that it is closely related to motor and cognitive impairment in the elderly. Iron imbalance and abnormal deposition are also involved in the pathogenesis of Alzheimer's Disease (AD) and motor neuron disease [7,8].

AD is the most common cause of dementia caused by molecular lesions, attributed to the aggregation of misfolded proteins, inflammation and metabolic failure, leading to neurological dysfunction [9]. The recognition that iron dysregulation is critical in AD pathology is based on the observation that patients have elevated iron levels in cortical, subcortical, and white matter areas affected by the disease [5,10,11]. Magnetic resonance imaging (MRI) analysis reveals that increased iron levels in the hippocampus, an important structure perturbed early in AD, negatively correlates with memory test performance [6]. Increased iron loading in the brain is also associated with beta-amyloid (Aβ) plaque formation in cortical e subcortical areas [5].

The dysregulation of iron metabolism in AD is accounted for in the current framework of the amyloid cascade hypothesis. Accumulating evidence suggests that impaired iron homeostasis is an early event in AD progression. Iron dysregulation leads to a loss of function in several enzymes, the formation of toxic oxidative species, and the elevated production of beta-amyloid proteins [12,13]. Thus, increased iron levels and its dyshomeostasis, that have been associated with AD, support a causative interplay between the concerted loss of iron homeostasis and amyloid plaque formation. We hypothesize that iron increase and beta-amyloid plaque pathology is synergistic in the process of neurodegeneration and ultimately cause a downward cascade of events that spiral into the manifestation of AD [14].

In the present study, we amalgamate recent findings of the brain iron metabolism in AD brains, as well as how disturbances in iron regulation lead to the etiology of the disease and spread the clinical conditions of AD. In addition, we reviewed studies assessing the relationship between brain iron accumulation and patients with AD (brain neurodegeneration studies that involve cognitive aspects). Finally, based on the findings, a state of the art for brain neurodegeneration and AD is provided, highlighting the main discoveries and limitations and addressing further directions, clinically relevant for neuroscience research.

Methodology

We conducted an integrative review. A computer-based literature search was conducted in two main databases - ISI Web of Science and PubMed (1990-present) - and it was initially performed in May 2017 and repeated in June 2017, using relevant search terms (such as. [Iron Accumulation and Alzheimer's disease]; [Alzheimer's disease and Neurodegeneration]).

Abstracts were examined for references to the research question and, if the study appeared relevant, then the full text was retrieved. Case reports, meta-analysis, experimental studies and reviews were included in this paper. Studies of neurodegeneration with brain iron accumulation in patients with AD were explored for inclusion in this integrative review. In summary, studies were included if they met the following inclusion criteria: a) Study design: clinical trials, preclinical basic research studies, and reviews studies; b) Population: study population composed of healthy individuals and/or individuals with AD (e.g., middle-aged adults and elderly); c) Intervention: histologic and MRI data in association with cognitive tasks. Criteria for exclusion were: (a) dissertations, book reviews, conference proceedings, or editorials. The results were analyzed, and papers that were deemed to be relevant and of an acceptable global quality were included in the analysis. Thus, in total, 27 studies were included in the review.

Results

We selected 27 studies about AD associated with Iron accumulation and neurodegeneration. Although the mechanisms of AD development are still being debated, a series of evidence supports the idea that metals, such as copper, iron, zinc, magnesium and aluminum, are involved in the pathogenesis of the disease [15]. AD is the most prevalent form of dementia in aged people, which is defined by two pathological characteristics: β-amyloid protein (Aβ) deposition and tau hyperphosphorylation. Moreover, the mechanisms of oxidative stress, synaptic plasticity, neurotoxicity, autophagy and apoptosis mediate the effects of metal ions-induced aggregation state of Aβ and phosphorylated tau in AD development. More importantly, imbalance of these mechanisms finally caused cognitive decline in different experiment models [16,17].

Despite the brain's highly regulated system for iron utilization and metabolism, disorders, such as AD, often present disruptions within iron metabolic pathways. Such dysregulation allows saturation of proteins involved in iron transport and storage, and may cause an increase in free ferrous iron within the brain, leading to oxidative damage. Not only do astrocytes, neurons, and brain endothelial cells serve unique purposes within the brain, but their individual cell types are equipped with distinct protective mechanisms against iron-induced injury [16,17].

Discussion

The iron is an important transition metal, which is responsible for a crucial paper in many chemical reactions, such as oxidative phosphorylation, myelin production or neurotransmitters synthesis and metabolism [1,2]. The iron´s homeostatic breakage promotes neurological deficiencies that are demonstrated in neuroimage studies in patients with AD, and eventually is based on observation of elevated iron levels in cortical and subcortical areas and white matter [18]. Greenough., *et al*. [19] has demonstrated raised iron levels in MRI, primordially in the striatum and hippocampus, which are important structures in the process of controlling executive functions and cognitive aspects, mainly the motor control and memory consolidation process and the conversion of short-term memory to long-term one, respectively.

AD is one of the most common neurodegenerative diseases, with multifactorial aspects, which causes accumulation of insoluble beta-protein and neurofibrillary tangles (NFTs), constituting the architecture of hyperphosphorylated tau protein precipitates, through the adjuvant action of the iron phosphorylation´s disorders in neuronal tissue [13]. One of the most important clinical clues for AD is the likely clinical history of insidious learning and memory difficulties that are sufficient to affect the performance of day-to-day activities [20]. In addition to the questioning of cognitive and motor deficits, a variety of other cognitive faculties is also deficitary, which includes reduced visual processing and language skills [21]. Pathologically, AD is highlighted by the degeneration of cortical and subcortical neurons, especially the dopaminergic neurons in substantia nigra pars compacta and hippocampus, as well as intracellular inclusions of the body of Lewy (LB), largely composed of α-synuclein. AD was traditionally defined by its characteristic marks of cognitive memory deficits and motor executions [22].

In patients with AD, iron accumulation is identified, being the highest iron´s concentrations evidenced in substance nigra, as well as in the areas of dopaminergic projection of the striatum, including the caudate nucleus and putamen [3,4]. Interestingly, these are the most vulnerable sites to neurodegeneration, underlying the parkinsonian phenotypes. However, it is well evidenced in the neuroimage of patients with AD, suggesting that the excessive accumulation of iron in these areas can contribute to neurodegeneration through the generation of oxidative stress and neuronal vulnerability [2,5]. Postmortem studies of patients with AD showed a selective and significant increase in total iron levels in brain tissue and a reduction in the ferritin´s immunoreactivity in substance nigra, suggesting the presence of senile plaques and neurofibrillary tangles in neuronal tissues [12]. In addition, iron-related oxidative stress has been shown to induce α-synuclein aggregation [8].

In addition, the genetic constitution predisposes to brain neurodegeneration in AD patients, through iron accumulation and high oxidative stress, inducing neuronal death and deficiencies in the connections associated with memory and executive actions [23]. Iron catalyzes the formation of highly reactive hydroxyl radicals through the Fenton reaction, increasing lipid peroxidation observed in the nigra substance of patients with AD [8,15]. Taken together, these findings show that homeostatic iron rupture leads to its accumulation in many brain regions, since it generates functional consequences in cognitive functioning [24]. The formation of the classic AD´s neuropathological traits influenced by iron metabolism is expressed, in particular, by the *APOE* gene, which modulates the expression of ferritin in phosphorylation cascades in neural tissues. Thus, it has been demonstrated that patients with AD, who have polymorphisms in the *APOE* gene, demonstrate elevated iron levels in the white matter of the brain. Compared to the control and associated with age´s variables, patients with AD show elevated levels of iron, zinc and copper in the cerebrospinal fluid and white matter [25]. In addition, iron concentration in the cerebral parenchyma is even higher in patients with AD, which is enriched by senile plaques and NFT, since it accelerates their aggregation and accumulation in amyloid plaques [26]. Thus, the synaptic iron dysregulation is particularly relevant for the cognitive impairment aimed at recruiting long-term memory and motor control [27].

Conclusion

AD´s physiopathology is multivariate, with numerous physiological characteristics correlated with its progression, based on essential metals' dysregulation in neurotransmission, in particular, the dysregulation of iron metabolism. Iron overload in the brain does not always lead to amyloidogenesis and AD, and conversely, the amyloidogenesis does not always lead to iron overload. However, studies support such association between iron deposition in brain tissue and amyloidogenesis and AD. In this context, the exact nature of this relationship remains unclear and encompasses multiple possibilities; the senile brain aspect may absorb more iron and predispose to AD, poor transport or incorrect release in iron-specific receptors, as well as genetic variations that modulate the phosphorylation and the cascade of iron´s release in tissues. In summary, the finding that the amyloid plaque is associated with iron dysregulation correlates well with the loss of memory and cardinal characteristics of AD.

Conflict of Interest

The Authors declare that there is no conflict of interest.

Authorship Contributions

A.M and M.O designed, developed the manuscript and wrote the initial manuscript. H.C, J.F, L.M, S.T, V.M and C.L.M. helped with editing, reviewing, scientific input, and final presentation. M.O teachers' advisor the work.

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