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Metal toxicity exposure in Alzheimer's disease- literature review

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ABSTRACT

Introduction and purpose: As the elderly population grows, the risk of cognitive decline and dementia increases. Environmental toxicants, including metals, have been identified as potential contributors to these conditions. This literature review investigated the potential contribution of metals, such as aluminium, lead, zinc and copper to Alzheimer's disease development.

Material and methods: The literature was conducted using "Pub Med" and "Google Scholar" databases with the keywords "metals", "Alzheimer's disease", "aluminium", "lead", "neurodegenerative diseases", "copper".

Brief description of the state of knowledge: Metals can negatively affect the functionality of the central nervous system, leading to impairments in behavior, motor skills, and cognitive abilities. The development of Alzheimer's disease can be influenced by several factors, including A β aggregates, tau tangles, synaptic dysfunction, inflammation, and oxidative stress, which may be worsened by interactions with these metals.

Results and conclusions: Extensive research has shown a link between metal exposure and neurodegeneration. Understanding the role of metals like lead, copper, aluminum, and zinc in Alzheimer's disease pathogenesis remains crucial, but further investigation is needed. A better insight into the impact of metal exposure on brain health could help find the way for effective prevention and treatment strategies for neurodegenerative diseases.

Keywords: metals; Alzheimer's disease; aluminium; lead; neurodegenerative diseases; copper

INTRODUCTION

Alzheimer's disease (AD) is a complex neurodegenerative condition influenced by multiple factors. Approximately 95% of all AD cases do not have an observable family history and are classified as "sporadic AD" (SAD). Alzheimer's disease is clinically classified into four stages based on the level of cognitive decline: preclinical, mild, moderate, and late-stage [1]. A

definitive diagnosis of AD typically involves the identification of β -amyloid ($A\beta$) plaques accumulating outside neurons and the presence of neurofibrillary tangles (NFTs) forming within neurons, both of which are prominent traits of the disease. AD progresses gradually, often beginning with mild cognitive impairment and advancing over time [2]. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) has indicated that it takes an average of six years for mild cases to progress to severe cases using the Clinical Dementia Rating Scale (CDR) [3]. In the advanced stages of AD, individuals experience a profound loss of cognitive abilities, personal identity, and everyday functioning [2]. According to the World Health Organization's (WHO) 2013 update on Alzheimer's disease (AD) epidemiology, the global prevalence of dementia is expected to triple by 2050 from approximately 35.6 million cases reported in 2010. Dementia, including AD, is strongly associated with advancing age, rising significantly among older individuals. While around 5-8% of people aged 65 and older are affected by dementia, this percentage increases to 25-50% in individuals aged 85 and above. These projections highlight the urgent need for effective strategies to address the growing burden of dementia on individuals, families, and healthcare systems worldwide [4]. Recent studies highlight the significance of epigenetic mechanisms, such as environment and lifestyle in shaping the connection between environmental exposures and Alzheimer's disease (AD). Specifically, exposure to environmental toxic metals has been linked to AD development. Humans encounter toxic metals from diverse sources such as diet and work-related exposures. These metals can potentially enhance the production of amyloid-beta ($A\beta$) and the phosphorylation of tau protein (P-tau), leading to the formation of amyloid plaques and neurofibrillary tangles (NFTs) [5]. Understanding the roles of metals in the development of Alzheimer's disease (AD) is crucial. In this article, we examine the literature concerning lead, zinc, and aluminum, and their potential connections with AD.

Fig.1 The influence of metals on brain tissue [38].

ALUMINIUM

Aluminum ranks as the third most common element found in the Earth's crust and with the most quantity. Due to its high reactivity, aluminum does not exist in its elemental form in nature. Still, it is rather found in combination with other elements such as hydroxide, silicate, sulfate, and phosphate. It's used in various products and sectors like preserving food, making cans, cookware, building cars, and even in vaccine adjuvants [6,7,8]. Aluminum toxicity causes oxidative stress that overpowers cell defenses, damaging vital components and disrupting cellular balance. It affects neurons, immune cells, and cells in organs. Moreover, it interferes with the ability of progenitor cells to multiply and function normally [8]. Aluminum induces protein oligomerization, delaying their breakdown and resulting in toxic accumulation within the brain. This leads to neuronal cell damage, disrupts enzyme activities in neurotransmitter synthesis, interferes with synaptic transmission via voltage-gated calcium channels and neurotransmitter receptors, and ultimately disrupts overall brain function by causing a signaling imbalance [9]. The symptoms caused by exposure to aluminum toxins include speech difficulties, dyspraxia, tremors, partial paralysis, and notable declines in learning and memory. Additionally, aluminum exposure has been linked to other health issues such as dialysis-related dementia, microcytic anemia, osteomalacia, and epilepsy [7]. A recent study has found that along with visual evidence of aluminum presence in brain tissue, there is a possibility that individuals with a genetic predisposition to Alzheimer's disease (AD) may also have a higher tendency to accumulate and retain aluminum in the brain. In cases of familial AD, where there are adjustments in the expression and metabolism of amyloid precursor protein (APP)- a gene that increases the risk of Alzheimer's disease, there is meaningful evidence involving amyloid-beta(A β) in the disease's development [10,11]. Aluminum is not naturally found in the human body's metallome but is widely present, particularly in the brain. It disrupts the body's processes without contributing to homeostasis, making it inherently harmful. Each aluminum atom present in brain tissue is highly reactive and poses significant biological risks. Therefore, it is crucial to set limits on its quantity and distribution. Raising awareness about human exposure to aluminum is also essential [12].

LEAD

Lead exposure raises a significant public health concern and accounts for approximately 1% of the global disease burden. It is particularly harmful to children and older adults. In children, long-term exposure to lead can result in cognitive and behavioral problems that persist into adulthood. Whereas, adults exposed to lead have an increased risk of developing various

chronic conditions, such as amyotrophic lateral sclerosis (ALS), Parkinson's disease, hearing impairment, age-related cataracts, glaucoma, and other chronic ailments. The primary sources of lead are electronic waste recycling, lead mining, and smelting. Children are particularly vulnerable to ingesting lead dust due to their frequent hand-to-mouth behavior. Older houses may still have lead pipes, which can lead to lead exposure through water ingestion by both adults and children. Industrial lead smelters and trash incinerators release lead into the local atmosphere as a by-product [13]. The oxidative stress induced by lead overload not only intensifies the aggregation of A β proteins but also damages neuronal cells, resulting in lasting deficits in intelligence and behavior. According to Bolin et al., exposure to lead during early life leads to the hypomethylation of the APP gene, causing its overexpression and increased production of amyloid precursor protein (APP). This, in turn, leads to the formation of plaque in the brain which triggers inflammation and neurodegeneration [14,15,16]. Research studies have shown that being exposed to lead (Pb) during the early stages of life can increase the levels of A β and APP in rats in later stages of their life. Interestingly, the long-term effects of Pb exposure on A β and phospho-Tau dynamics vary depending on exposure time. Exposure to Pb during the early stages after birth and continuous exposure from birth can increase the levels of A β and phospho-Tau in the hippocampi of mice, leading to poor learning and memory abilities. However, exposure to Pb in adulthood does not result in the same effects [17]. Lead enters the body and gets absorbed into cells and tissues. It damages the lungs when inhaled and enters the bloodstream by three primary routes: the lungs, intestines, or skin. Adults absorb 10-15% of consumed lead, while pregnant women and children can absorb up to 50%. Diet, genetic factors, and occupation influence the amount of lead absorbed [18]. It is a fact that there exists no level of lead exposure that can be considered safe [19].

ZINC

Zinc is an essential mineral for both humans and organisms. It is absorbed in the small intestine and gets eliminated through various processes. Zinc plays a crucial role in neuroprotection, immune and brain function. If you have a zinc deficiency, it can lead to immune impairment, cognitive dysfunction, and impaired skin and bone development. Zinc also plays a significant role in neurodegenerative diseases like Alzheimer's, Parkinson's, and multiple sclerosis. It modulates synaptic receptors and is stored in synaptic vesicles of glutamatergic neurons. Disruptions in zinc homeostasis contribute to disease pathophysiology and affect cytokine production during inflammation. Zinc ion (Zn²⁺) contributes to

Alzheimer's disease (AD) at the predementia stage. It modulates glutamate, a crucial neurotransmitter, and is found in synaptic vesicles. Zinc transporters play a vital role in regulating the movement of zinc across membranes, maintaining optimal zinc homeostasis both at the cellular and systemic levels. Evidence supporting the connection between Alzheimer's disease (AD) and metal dysregulation has been found in post-mortem analyses of amyloid plaques, which indicate three times greater zinc buildup and decreased levels of the synaptic zinc transporter in comparison to normal brains [20,21,22]. According to research, individuals with Alzheimer's disease have been found to have lower levels of zinc in their plasma as compared to healthy individuals [23]. The role of zinc (Zn) in Alzheimer's disease (AD) is unclear and has led to conflicting findings. Zinc levels decrease as we age, which may result in oxidative stress, inflammation, and memory decline. Some studies have linked high zinc intake to AD and cognitive decline, while others report decreased zinc levels in AD patients without significant cognitive changes. This discrepancy may be due to zinc's dual role in promoting amyloid plaque formation at low levels and contributing to Tau protein phosphorylation at high levels, both of which are characteristics of AD [24]. Although zinc is essential for normal brain function, too much or misplaced zinc can cause significant harm to brain cells. Excess zinc can increase protein deposition, stick to A β , exacerbate neuron damage, and lead to the clumping of tau proteins, resulting in the formation of harmful tangles in the brain. However, reducing zinc levels has been shown to reduce the formation of harmful tau tangles, which highlights the importance of maintaining optimal zinc regulation for brain health. By being mindful of zinc intake and ensuring proper regulation, we can promote healthy brain function and help prevent the onset of diseases like Alzheimer's [25].

COPPER

Copper is an essential element found in the brain, liver, and kidneys, it is playing an important role in various bodily functions like red blood cell formation and bone health. It is a co-factor for enzymes and transitions between oxidative states, performing activities such as energy metabolism, iron regulation, antioxidative activity, neurotransmitter synthesis, and myelination. It's crucial for lung function and cellular respiration, stored in the body for protein and energy production. Although copper is important, excessive amounts can lead to oxidative stress, which can harm the body. Healthy copper levels range from 50 to 80 mg. Exceeding this range can be toxic, causing issues like liver cell death, nerve damage, and reduced cell growth [26,27]. Copper does not interact with amyloid beta (A β) until A β is

released from the amyloid precursor protein (APP). Once A β is released, copper and A β bind together strongly. This interaction affects how A β forms amyloid plaques, which are associated with Alzheimer's disease (AD). Additionally, the protein tau forms tangles in AD brains and may also interact with copper. Although it is unclear whether these protein clumps cause AD or are merely a side effect, they are always present in AD brains. Therefore, we need to understand how they form and how copper plays a role in A β toxicity and AD development [28]. On the other hand, It has been hypothesized that Alzheimer's disease may be caused by a lack of copper in the body. Several brain regions previously found to be affected in AD brains showed decreases in Cu levels. People with the disease tend to weigh less than usual and lose weight before their memory declines. This weight loss is linked to more severe symptoms. Poor nutrition can make the condition worse. Copper is needed for the activity of cytochrome oxidase, which is important for brain function. People with Alzheimer's disease have lower levels of copper in their brain [29,30,31].

DISCUSSION

Extensive research has confirmed the link between exposure to metals and neurodegeneration, which is a significant concern for public health. With the increasing frequency of dementia and worsening environmental pollution, this issue has become more critical than ever. Metals disrupt the normal functioning or structure of the central nervous system, leading to cognitive, motor, and behavioral impairments, as well as mental disorders. [32]. Alzheimer's disease is a complex disorder with diverse symptoms reflecting multiple factors, recent research suggests that several different metals, including lead, aluminum, copper and zinc interacting with each other might be responsible for causing it. Key features include A β aggregates, tau tangles, synaptic dysfunction, inflammation, and oxidative stress. Neurotoxicants disrupt pathways, balance in our cells, induce stress, trigger inflammation, and lead to neuronal death, contributing to AD progression. This connection is crucial for future research and management of AD and related disorders [33,34]. Alzheimer's disease (AD) affects how copper is stored in the body, leading to an imbalance in copper levels between the brain and blood. Copper deficiency in the brain contributes to the harmful production of amyloid, which is responsible for the formation of amyloid-copper complexes. These complexes are formed due to higher levels of copper and amyloid, and the strong affinity of amyloid peptides for copper. Addressing the cause of copper deficiency in brain cells is crucial to understanding AD pathology [35]. Zinc deficiency may be linked to neurodegeneration, which could be

influenced by dietary factors. Even though zinc has also been suggested in many researches as a possible risk factor for Alzheimer's disease, the role of this metal in A β aggregation is unclear, with some studies showing promotion and others showing inhibition. The efficacy of zinc supplementation in patients with Alzheimer's disease is still uncertain due to conflicting results reported in studies. Some studies have suggested that zinc supplementation may improve cognitive function and delay the progression of Alzheimer's disease. However, other studies have reported no significant benefits of zinc supplementation in Alzheimer's disease patients [34,36]. Because of the complexity of the disease pathogenesis, there is a necessity for continued investigation into the precise mechanisms underlying zinc dysregulation in Alzheimer's disease and its potential therapeutic implications. The role of Zinc in Alzheimer's disease is controversial and requires further study [13]. The role of metals in neurodegeneration has gathered increasing interest in neuroscience, as metal imbalances have been strongly linked to neuropathology. Although metal toxicity has been extensively studied, there are still crucial aspects of this topic requiring further investigation to shed light on the complex relationship between metals and neurodegeneration, with the ultimate goal of developing effective treatments and preventive strategies for Alzheimer's disease and other neurodegenerative conditions. [32,37].

CONCLUSION

The review was based on the present literature view and concluded that the latest observations show that exposure to certain metals may increase the prospective risk of developing such diseases. This is an important finding that highlights the need to further investigate the potential link between metal exposure and the development of neurodegenerative diseases. This article aimed to highlight the possible correlation between aluminum, lead, zinc, copper and Alzheimer's disease based on the present literature view. Latest observations indicate that exposure to certain metals may increase the prospective risk of neurodegenerative diseases like Alzheimer's disease (AD).

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