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Aluminum toxicity induced Alzheimer's Disease and its potential treatment using antioxidants - a review

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Over the years, a handful of drugs have been approved to be used in the fight against Alzheimer's Disease but unfortunately none of these drugs have proven to be solid-treatments. Alzheimer's Disease is one of the most prominent diseases observed in the elderly population. In this review article, we discuss how aluminum toxicity can lead to neuro degeneration. Aluminum is abundantly present on the earth's crust and hence becomes easily accessible to man. This makes it an obvious choice in the preparation of numerous substances, packaging, etc. Such wide usage of the metal can pave an easy access to the body, leading to toxicities. Aluminum toxicity has been linked to oxidative stress which has an established relation with neurodegeneration and mitochondrial damage. We also discuss how consumption of antioxidants can be useful in combating oxidative stress.

Keywords: Alzheimer's Disease. Aluminum. Toxicity. Oxidative stress. Neurodegeneration.

INTRODUCTION

As people age, their health deteriorates which may lead to numerous health complications with memory impairment being one of the most common ones. According to the World Health Report of 1998, it was estimated that a major portion of the aged population would be suffering from Alzheimer's Disease by 2020, and interestingly that turned out to be true(Mathuranath et al., 2012). The exact etiology of the disease still remains debatable but studies have suggested factors such as senile plaques, which are composed of \Box - amyloid and intracellular neurofibrillary tangles, are responsible for the onset of Alzheimer's Disease. Another protein called apolipoprotein E, or apo E allele, accelerates the onset of the disease; various genetic factors have also been found to be directly or indirectly involved in the etiology of the disease. Oxidative stress hypothesis suggests that

free radicals may act as a potential causative agent of Alzheimer's Disease (Pereira *et al.*, 2005).

Heavy metals have had a well-established impact on the development of the brain. Amongst the commonly available alzheimerogenic chemicals, heavy metals have shown great effectiveness in inducing the disease on being exposed for long durations. Countless studies involving the linkage between aluminum and Alzheimer's Disease have been performed which have suggested the effectiveness of aluminum in inducing Alzheimer's Disease(Mahdi et al., 2019). Numerous studies have revealed elevated levels of aluminum in the brain of patients experiencing memory deficit. Extensive animal studies have suggested time and again that excessive aluminum consumption can affect the central nervous system. Histopathological and microscopical reports are evident that the changes observed are similar to human senile dementia as observed in Alzheimer's Disease.

However, a solid relationship between aluminum and Alzheimer's Disease is yet to be established, although its known that aluminum induces oxidative stress as well, epidemiological studies have suggested that elevation

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in the level of aluminum can be linked to Alzheimer's Disease. In this review, the potential neurodegenerative effect of aluminum will be discussed.

Aluminum induced Alzheimer's Disease

Alzheimer's Disease

Alzheimer's Disease (AD) is one of the major causes of dementia. It is estimated that the number of patients suffering from Alzheimer's Disease at present may triplicate in the next 50 years if left unchecked (Goedert, Spillantini, 2006). Hence, scientists are working tirelessly to come up with a cure. By 2025, the estimated number of AD patients in the developed society may go up to 22 million (Van Der Zee, Sleegers, Broeckhoven, 2008). Clinically, AD is associated with memory impairment, cognitive dysfunction, behavioral changes, etc. all of which may affect the daily life of an individual. In the end-stages of AD, patients may require custodial care for constant monitoring. The neuropathology of AD revolves around numerous factors like senile plaques of β -amyloid peptide, neurofibrillary tangles (NFT) that are made of hyperphosphorylated tau protein, in conjugation with ubiquitin(Bertram, Tanzi, 2005). These clinical diagnostic features are generally restricted to two regions of the brain, namely- the hippocampus, the memory center and the cerebral cortex, the center for reasoning, language, memory, etc. It has been observed in AD, there is a reduction in the size of the brain due to death of neurons and degradation of synapses. AD is linked to at least three genes encoding the amyloid precursor protein (APP) among those presenilin 1 and 2 on chromosome 14 and 1, respectively. In AD cases presenilin mutations occur are more frequent than those with APP mutations. (Annaertet al., 2006)

It is evident that most of the cases are sporadic and not familial, meaning the chances of developing the disease are much higher based on our environment, lifestyle choices, etc. and not much with respect to family history; however, families with a history of sporadic AD patients have higher chances of developing the disease (Alonso, Vilatela, López-López,2012).

One of the major causes of the disease is heavy metal toxicity. Various heavy metals like cadmium,

lead, iron, aluminum, etc. have been constantly linked to Alzheimer's Disease. Our environment is filled with pollutants and industrial waste, this increases our chances of developing the disease. Aluminum has been used widely as a neurotoxic agent in variousstudies to induce Alzheimer's Disease (Lee, Park, Seo,2018).

Aluminum

Being one of the most abundant elements in the planet's crust, aluminum can be easily detected in our surroundings, be it drinking water or medicines (Aguilar et al., 2008). These factors make us very prone to aluminum consumption. As per the European Food Safety Authority (EFSA), a tolerable weekly intake (TWI) has been set. According to the EFSA, TWI of a 60kg adult is 1mg Al/kg body weight, Relative exposure in children is higher at up to 2.3 mg/ kg body weight/ week. However, exceeding these values does not indicate in any sort of acute danger. The dangers of aluminum exposure are greatly dependent on the route of exposure. Aluminum exposure via gastrointestinal tract (GI) and intact skin is very mild, hence TWI can only be used to provide an idea about the person's aluminum exposure. Determination of aluminum via blood or urine is considered to be a better alternative to assess one's level of aluminum toxicity.

People working in aluminum welding or aluminum powder industries have shown significant urine and blood toxicity levels in the long run(Kiesswetter *et al.*, 2007). In these patients, absorption from nasal cavity may be a prominent site for aluminum exposure. Studies have shown that the olfactory neurons within the nasal mucosa act as a major site which exposes the CNS to the environmental aluminum. Having been exposed to aluminum for so many years, the gradual accumulation of the toxicant has suggested the increase in the risk of developing various neurodegenerative diseases and cancers in the workers (Yokel, 2000).

Aluminium exposure to the brain

Studies have suggested a number of ways through which aluminum can enter the brain; these may include

the nasal route, the BBB or through the choroid plexus (CP). It has also been revealed that aluminum is most often absorbed from the GI tract or lungs. Patients who had undergone brain surgery after consuming antacids which were Al-rich had shown higher concentrations of Al in their brain in comparison to those who had consumed less Al containing antacids, this gives us an idea about the oral absorption and distribution pattern of Al in normal renal functioning cases. The CP is present in the third, fourth and each of the two lateral ventricles of the brain. This is a site where most of the Cerebrospinal fluid (CSF) is produced. A substance is able to enter the CSF via the CP. Certain number of experiments have revealed that in normal patients and patients suffering from neurodegenerative diseases, the CSF-Al concentration was ranging from <1 to 6 μ g/L, whereas in three Al-intoxicated patients the concentration was found to be comparatively higher, 3 to 7 μ g/L(Van Landeghem et al., 1997; Kapaki et al., 1993).

Over the years, a number of studies have suggested a direct link between Al- brain content and age(Morita *et al.*, 2001). As a person ages his/her susceptibility to aluminum in the brain may increase due to a number of factors like weakened BBB, slow or no elimination of brain Al. However, the rate of elimination of Al from the entire body may dictate the rate of Al clearance from the brain, as an equilibrium must be maintained amongst the various Al storage compartments. About 58% of human Al concentration can be found in the skeletal muscles(Krewski *et al.*, 2007).

Oxidative stress induced Alzheimer's Disease

As we have studied above, the primary route for Al excretion is via urine. Hence, it has been observed that subjects with immature or malfunctioned kidneys may experience excessive accumulation of Al in the body(Yuan,Hsu, Lee,2011). In certain cases of neonates, due to underdeveloped kidney, BBB, etc. high intake of aluminum containing substance may lead to aluminum toxicity in the brain. However, increased Al content in the brain may lead to excessive free radial formation.

The brain is susceptible to oxidative damage due to excessive oxygen activity and low antioxidant

enzyme activities, a high concentration of Al can only worsen the situation. Aluminum despite having low redox potential may cause oxidative damage through a number of ways, it can cause the stimulation of iron related lipid peroxidation in the Fenton's reaction or it may bind to negatively charged phospholipids in the brain which would potentially lead to an attack by ROS (Verstraeten *et al.*, 1997; Exley, 2004). These ROS may cause cellular damage by oxidizing amino acid residues on proteins, leading to the formation of protein carbonyls. Free radicals play a vital role in the commencement of Alzheimer's Disease. Aggregation of \Box amyloid proteins may further accelerate the free radical formation (Christen, 2000; Yuan, Lee, Hsu, 2012).

Other potential neurotoxic metals

Metal deficiencies can lead to neurological disorders. For example, iron deficiency is related to pediatric stroke, restless leg syndrome, etc. However, these metals are required only in trace amounts. When present in excess, these metals can accumulate in various organs, including the brain, and lead to complications by causing oxidative stress, autophagy dysregulation, mitochondrial dysfunction, DNA fragmentation and activation of apoptosis. These abnormalities can eventually lead to neurodegeneration and either initiate or accelerate the progression of Alzheimer's Disease, Amyotrophic Lateral Sclerosis (ALS), Huntington's Disease, Parkinson's Disease, etc. (Chen, Miah, Aschner, 2016)

Some of the metals that can lead to neurodegenerative disorders are listed as under:

Essential metals:

 a) Copper (Cu): Copper is an essential trace element which is required for various physiological functions such as oxygen and electron transportation, protein modification, etc. However, in high amounts, Cu may result in ROS generation, DNA damage and mitochondrial dysfunction which may ultimately hamper neurotransmission and lead to neurodegeneration. (Desai, Kaler, 2008)

- b) Iron (Fe): Iron is an essential element that serves as a cofactor for a variety of proteins, most prominently in hemoglobin. Our body's exposure to Fe is mainly through the food we consume; however, toxic levels of Fe are achieved due to disrupted Fe homeostasis and metabolism. Hemolysis in the young brain with immature BBB can lead to abnormal iron accumulation, resulting in neuronal damage due to high ROS levels, lipid peroxidation, dopamine autoxidation, mitochondrial fragmentation. Fe dyshomeostasis has been linked to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease and also NBIA or neurodegeneration with brain iron accumulation. (Biasiotto *et al.*, 2016)
- c) Manganese (Mn): Low concentrations of Manganese serves as a cofactor in a variety of metalloproteins, including Manganese superoxide dismutase (MnSOD)and arginase, and is required in the functioning of various enzymes. However, when exposed to higher concentration of manganese, it may lead to mild complications during critical stages of development. Chronic Mn exposure may lead to a type of parkinsonism called Manganism. Elevated Mn levels has also shown to disrupt various cellular processes, increased ROS production, autophagy, etc. (Kwakye *et al.*, 2015).
- d) Zinc (Zn): Zinc is another important trace element required for various bodily processes and functions. Just like the previous metals, Zn when present in excess can lead to unwanted complications and suppression of Cu and Fe absorption, increased ROS production and disruption of metabolic enzymes. At low levels, Zn can suppress b-amyloid but at large concentrations, Zn enhances fibrillar b-amyloid aggregation, leading to neurodegeneration. (Hambidge, Cousins, Costello, 2000; Mizuno, Kawahara, 2013).

Non-essential metals

- a) Arsenic (As): Arsenic is a well-known toxic metalloid as well as a carcinogen. Our body's exposure to arsenic may lead to mitochondrial oxidative stress, imbalance of cellular Ca²⁺, abnormal ATP production, altered membrane potential, etc. Early exposure to As has been associated with lowering brain weight and reduction in neurons and glia; eventually leading to neurodegenerative disorders like AD and ALS. (Zarazúa *et al.*, 2011; DeFuria, Shea, 2007).
- b) Lead (Pb): In humans, lead exposure is mainly via inhalational or oral ingestion. Once in the body, Pb can bind toRed blood cells (RBCs) and accumulate in the bone. The primary target of Pb induced toxicity has been found to the nervous system. In the brain, hippocampus is the main location for Pb accumulation. Studies have suggested that Pb leads to deficits in memory, intelligence, language, emotions and even motor skills. (Mason,Harp, Han,2014).

c) Cadmium (Cd): Cadmium is a well-known carcinogen that enters the PNS and CNS subsequently damaging the BBB. In the cellular dynamics, Cd has been found to induce oxidative stress, inhibit DNA damage repair and apoptosis. Chronic exposure to this metal may disrupt the functioning of the nervous system leading to diseases such as AD and PD. (Wang, Du, 2013). The regulatory level of heavy metals mentioned by

US Environmental Protection Agency (EPA) more than that is considered as toxic dose.(Godwill *et al.*,2019).

Table I - Regulatory limit of selected heavy metals. ppm, parts per million; mg, milligram; EPA, Environmental Protection Agency; OSHA, Occupational Safety and Health Administration; FDA, Food and Drug Administration.

Antioxidant treatment



FIGURE 1 - Probable role of Antioxidants in the management of Alzheimer's Disease.

Antioxidants are endogenous or exogenous compounds exhibiting a variety of actions like scavenging and inhibiting ROS formation or binding to metal ions required for ROS generation. Antioxidants are being scrutinized time and again for their potential role in treatment and management of various neurodegenerative diseases (Gilgun-Sherki, Melamed, Offen, 2003a). Antioxidants like Vitamin E or α -tocopherol, Vitamin C and □-carotene may decrease free radical- induced damage in neuronal cells and inhibit the pathogenesis of various neurodegenerative disorders. Vitamin E is the most important lipid phase antioxidant making it highly lipid soluble. Studies have shown the effectiveness of vitamin E in attenuating the toxic effects of \Box -amyloid and improving the cognitive performance of rodents (Grundman, 2000). Vitamin C is another strong antioxidative agent which plays a major protective role against free radicals in the blood and plasma. In a study it was found that vitamin C was able to decrease

 α -tocopheroxyl radicals in membranes to regenerate α -tocopherol in return. Carotenoids are another group of lipid-solubleantioxidants which have shown impressive results in reducing lipid peroxidation and antioxidant activity. \Box -carotene is the most widely studied carotenoid due to its increased potency.

However, it is not completely clear if nutrient therapy can be helpful in the treatment of Alzheimer's Disease. Potent antioxidants like vitamin E have failed to reduce oxidative stress for half of the Alzheimer's patients in some trials. Other studies have reported that intake of antioxidant rich diet may not actually decrease the chances of developing the disease in humans, indicating that impressive results were obtained only in preclinical trials and very little has been achieved in human studies. Thus, future trials must be more precise and vigorous as we may still have a chance with antioxidants. Other agents like vitamin B_{12} may be studied because of their role in increasing the acetylcholine transferase activity in the cholinergic neurons and in turn improving cognitive functions as seen in cats and AD patients(Gilgun-Sherki, Melamed, Offen,2003b).

TABLE I - Numerous antioxidants have proven to be useful in countering the heavy metal induced toxicities, some of which have been mentioned in the table.

Sl. No.	Antioxidant plant source/ agent	Toxic metal	Reference
	Arthrospira maxima	Cadmium	(Argüelles-Velázquez etal., 2013)
	Nigella sativa seed oil	Cadmium	(Mohammed <i>et al.</i> , 2014)
	Allicin	Cadmium & lead	(Shahsavani et al., 2011)
	Annona muricata leaves	Arsenic	(Jomova et al., 2011)
	Hippophaerhamnoides	Arsenic	(Gupta, Flora, 2005)
	Quercetin	Arsenic	(Hertog <i>et al.</i> , 1995)
	Solanumnigrum &Solanumtrilobatumleaves	Lead	(Chinthana et al., 2012)
	Geitlerinemaamphibium	Aluminum	(Pradhan <i>et al.</i> , 2020)
	Salacia oblonga	Aluminum	(Nathiya, Nandhini, 2014)

CONCLUSION

Alzheimer's Disease is one of the most common neurodegenerative diseases. The patients have to undergo a lot of difficulties and require constant monitoring as they may harm themselves without even knowing. Heavy metals like aluminum may play a major in the pathogenesis of the disease. As promising antioxidants are on paper, only few positive results have been achieved in the treatment of AD, but we must understand that with a wider range of methodologies and with constant efforts we may still have a chance to get better results. Thus, with wider range of extensive studies we may discover the treatment of Alzheimer's Disease at the earliest.

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LIST OF ABBREVIATIONS

Sl. No.	Abbreviation	Full form	
1	AD	Alzheimer's Disease	
2	PD	Parkinson's Disease	
3	NFT	Neurofibrillary Tangles	
4	EFSA	European Food Safety Authority	
5	TWI	Tolerable Weekly Intake	
6	GI	Gastro-intestinal tract	
7	BBB	Blood Brain Barrier	
8	СР	Choroid Plexus	
9	Al	Aluminum	
10	CSF	Cerebrospinal Fluid	
11	ROS	Reactive Oxygen Species	
12	MnSOD	Manganese superoxide dismutase	

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