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NEUROTOXICITY OF ALUMINIUM: A COMPREHENSIVE REVIEW

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ABSTRACT

Aluminium is one of the major environmental neurotoxin, whose exposure produces several adverse effects. The severity of damage depends on the time and levels of exposure, the rate of absorption, individual susceptibility and the route by which the metal is absorbed. Aluminium has been reported that it can lead to Alzheimer's disease despite the controversy around the issue. When aluminum is absorbed into your brain, it lasts over a very long period and the half-life is reported to be 20% of lifetime. Although the precise cause of aluminium toxicity is unclear, the studies indicate that aluminium can enhance the inflammatory and oxidative events resulting in the synthesis of reactive oxygen- species and the degradation of antioxidant defense enzymes, which contribute to increased mitochondrial oxidative stress. This review attempts to describe the causes of exposure, symptoms of toxicity and molecular mechanisms by which neurotoxins can cause neurotoxicity, prevention and treatment for the aluminium induced neurotoxicity.

Keywords: Neurotoxin, Aluminium Neurotoxicity, Mechanisms, Symptoms, Prevention and Treatment, Neuroprotective Agents

1. INTRODUCTION

The nervous system consists of brain, spinal cord and huge network of nerves and sensory organs that are responsible for managing the major functions of the body. Though nervous system has defense mechanisms, it is moderately vulnerable to certain toxins, chemicals and other physical and biological agents as it causes destructive functional change in the nervous system by interacting with the neurons **[1]**. The toxins that are disastrous to the nerve tissue are called as Neurotoxinsand are responsible for the toxicity of the nervous system. Neurotoxicity is defined as the ability of chemical, biological, or physical agents to produce adverse functional or structural changes in the nervous system during development or at maturity. The patterns of the toxicity of neurons are: Neuronopathy, Axonopathy, Myelinopathy, Transmission toxicity **[2]**.

2. NEUROTOXIN:

Any substance from an exogenous origin entering the body by environmental sources leading to the damage of systemic or functional elements of the nervous system is subjected to have a neurotoxic capacity and is called as Neurotoxin. Substances that had polluted our environment and is hard for public to avoid exposure includes: Mercury, Lead, polychlorinated biphenyls, Insecticides, ethanol, nitric oxide, botulinum toxin, tetrodotoxin, Cadmium, Al, Solvents, Chlorine, Car exhaust, Formaldehyde, Phenol. More than 80,000 synthetic chemicals were raised in to our environment and less than 22% were properly tested. Over 1,000 of those tested are subjected to have neurotoxic effects **[3]**. Neurotoxins may damage neurons, axons, and/or glia leading in depletion of particular nuclei and/or axonal tracts or demyelination and also produce metabolic variations that may damage the central nervous system (CNS). The reaction of the body to neurotoxins are governed by (a) Damage to neurotransmitters, (b) Cellular membrane integrity and (c) Presence of the detoxifying mechanisms. A compound could be safe and useful at one concentration, but neurotoxic at other. Vitamin A and B_6 are necessary in the daily food in small amounts, but both produce neurotoxic reactions in larger amounts **[4]**.

Heavy metals and synthetic compounds with neurotoxic abilities.

Table 1: Neurotoxic agents and their Effects

Substance	Primary Neurotoxic Effects
Acrylamide	Injury of peripheral nerves, Muscle weakness, Numbness of limbs [5]
Arsenic	Altered mental state of mind, Injury of peripheral nerves (Degeneration of axons) [6]
Al (Al)	Oxidative stress, inhibited AChE activity, generation of Reactive Oxygen Species (ROS) [7]
Barbiturates	Malfunction of brain, developmental neurotoxicity, promoted neurotransmission of gamma aminobutyric acid. [8]
Copper	Wilson’s disease, Acute peripheral neuropathy.
Doxorubicin	Cerebellar ataxia, degeneration of sensory neurons [9]
Iron (Fe)	Altered transcripting activity, dysfunction of signal transduction
Lead, inorganic	Death of peripheral neurons (demyelination), altered mental status, cognitive impairment [10]
Mercury, inorganic	Middle cerebral artery syndrome, Emotional disorders, Excitotoxicity, Memory loss. [11]
Zinc	Production of ROS, Axonal mitochondrial dysfunction. [12]

2.1 Vulnerability of the Nervous system to Neurotoxins

Nerve cells are distinct in that they are ineffective of regeneration after a toxic injury to the brain, resulting in the greater impact on the neuronal system by the neurotoxins. Vulnerabilities of the different cells of the system determine the impact of biological markers when unveiling to a specific neurotoxic chemical. For example, exposure of triethyltin or hexachlorophene causes myelin degeneration indicating as spasticity. Neurotoxic effects are usually diagnosed by Computed Axial Tomography and Positron-Emission Tomography (CAT and PET scanning), electrophysiology, and Magnetic Resonance Imaging (MRI) **[13]**.

2.2 General Mechanism of Neurotoxicity: The following fundamental processes result in toxic injury to the nervous system:

1. Toxic damage and destruction of neurons and glial cells.
2. Disruption with electrical transmission.
3. Disruption with chemical neurotransmission.

Toxic damage and destruction of neurons and glial cells: Anoxia, an insufficient oxygen supply of the cells, or the inability to use oxygen has been the most leading cause for destruction of nerve cells and glial cells. Substances like carbon monoxide, hydrogen cyanide and hydrogen sulfide can pass through the blood-brain barrier and is quickly absorbed by neurons and glial cells resulting in altering the metabolism of cells and inhibiting the use of oxygen where the nerve cells lack oxygen and leads to death. Axons usually start to die at the axon's very distal end with necrosis moving steadily towards the cell body. This is called as "dying-back neuropathy" **[14]**.

Disruption with electrical transmission: There are two fundamental ways in which a toxic chemical may disrupt or interact with the distribution of the electrical potential (impulse) down the axon to the synaptic junction

1. Interfering with the action potential motion down the whole axon.
2. The Axon or its myelin coating causes structural damages. It will not be feasible to transmit the power without an intact axon.

The diffusion of electrical potential is blocked by compounds capable of resisting or inhibiting sodium and potassium channels, and sodium-potassium pump. It will decline, delay, or totally disrupt the electrical potential motion.

Disruption with chemical neurotransmission: A popular mechanism for the toxicity of a broad spectrum of chemicals is synaptic dysfunction. The basic principle for transmission of chemical is between two neurons and between a neuron and a muscle cell. Acetylcholine is the neurotransmitting chemical between a neuron and a muscle cell, whereas the several other kinds of neurotransmitting chemicals are associated between two neurons **[15]**.

3 NEUROTOXICITY OF ALUMINIUM

The third most copious metal is Aluminium (Al), which makes up approximately 8 percent of Earth's crust and a noticeable element in the periodical table. It is one among most frequently researched toxic metals, which is associated in several diseases. Human exposure to poisonous metals can harm a range of organ structures. It is widely used in regular life and was likely observed in drinking water by treatment of water for purification purposes **[16]**. On a daily basis, most adults consume 3-5mg of Al. Al's toxicity is promptly associated with its bioavailability. The brain is regarded to be the most susceptible to the Al toxicity and is particularly susceptible to oxidative stress leading to enhanced concentrations of free radicals and reduced concentrations of antioxidants **[17]**. Because of its interaction with metabolic enzymes engaged in various processes, Al is regarded as a strong neurotoxic agent in both humans and animals. Al has been shown to accumulate in several mammalian tissues such as brain, bone, liver and kidney in biological systems, the elimination of Al from the brain is determined as seven years.In specific, Al exerts both immediate geno-toxicity in human neural cells and induces neurodegeneration by increasing the output of Fe accumulation and Reactive Oxygen Species (ROS). Al-induced oxidative injury to DNA has earlier been linked with neurodegeneration in various rat brain areas and currently, Al^{3+} in the nematode *Caenorhabditis elegans* was shown to cause transporter-mediated dopamine neuron degeneration **[18]**.

3.1 Exposure of Humans to Aluminium

Aluminium (Al) based objects are strong, durable, light and resistant to corrosion and are a good conductor of electricity. This is why Al is found in almost all aspects of our everyday life **[44]**. The current industrial products of the 20th century carrying Al salts such as antiperspirants are another cause of expose **[19]**. In terms of bioavailability, owing to its activity as a flocculant, Al is now discovered in drinking water, and is a frequent ingredient in numerous processed products, which is also incorporated in cosmetics of many kinds, and pharmaceutical products. As a consequence, Al is increasingly observed in our bodies in the human environment. Exposure of Al is reported to build up in several organs, including bone, liver and spleen through inhalation, ingestion and contamination of intravenous fluids **[20]**. Persons with renal impairment are highly susceptible to the neurotoxicity.

3.2 Clinical Symptoms

The Al toxicity is unspecific by its signs and symptoms. Though acute toxicity is associated with the constipation, anorexia, anemia, osteoporosis nausea and gastrointestinal irritation. Long term exposure of Al results in damage of neurons and symptoms includes:

Altered mental status, confusion, muscle weakness, bone pain, deformities, and fractures, seizures, speech problems, muscle twitching, numbness and slow growth in children. Complications include impaired iron absorption, bone problems, lung problems, skin diseases, anemia and neurodegenerative diseases like Alzheimer's Disease (AD) and Parkinson's Disease **[21]**.

4 MOLECULAR MECHANISMS OF ALUMINIUM NEUTOTOXICITY

There is no specific mechanism through which the Al causes neurotoxicity but there are numerous characteristic factors are involved in leading to the neuronal death. Although Al is poorly absorbed in the Gastr o Intestinal Tract (GIT), inhalation facilitates the immediate transfer of Al to the brain via the olfactory system **[22]**. The mechanisms underlying the Al neurotoxicity are as follows:

ROS formation: Al can also result in lower production of axonal mitochondria' which causes the release of oxidative substances like malondialdehyde (MDA) and enzymes like super oxide dismutase (SOD) into the neurons, leading to higher development of free radicals derived from oxygen. Progressive mitochondrial dysfunction results from excessive free radical yield, which then affects other biological molecules and stimulates LPO. Al^{3+} ions react with the hydrogen peroxide (H_2O_2) to form Al superoxide radicals (AlO_2^-), which depletes the mitochondrial iron and promote formation of ROS further leading to neuronal damage or neuronal death **[23]**.

Oxidative stress: Al is not a transition metal that immediately initiates Lipid peroxidation (LPO) but it enhances the oxidative characteristics of transition metals such as iron and copper.Al^{3+} ion is about the same size as Fe^{3+}, occupying iron locations in the transfer of iron transport protein transferrin and is circulating throughout the body with ease **[24]**.

Increased AChE activity: Al works as a significant Ethylcholine Mustard Aziridinium ion (AF64A), a Cholinotoxin leading to neurochemical and neuroanatomical brain alterations. The biphasic impact of Al on the activity of Acetylcholinesterase (AChE) initially increases the enzyme's activity during the first 4–14 days of the exposure accompanied by a significant reduction. The slow Al accumulation in the brain was the result of this biphasic effect. Enhanced AChE activity results in the breakdown of the ACh leading to the declined ACh levels and impairing cholinergic functions in the brain **[25]**.

Phosphorylation of tau protein: Research findings have highly correlated the developing symptoms of AD like accumulation of hyper phosphorylated tau-protein consisting of neurofibrillary tangles (NFTs) and the retention of insoluble amyloid-β (Aβ) proteins as Aβ plaques with the accumulation of Al in the brain but cannot exit, therefore its concentration in the brain rises progressively with age. Al becomes neurotoxic by triggering the accumulation of neurofibrillary tangles and impairment of motor function of neurons **[26]**.

5 RESPONSES ASCRIBABLE TO ALUMINIUM

The significant pathways through which Al is subjected to have a biochemical impact are known to be bio diversely accessible and are intended to produce biochemical impacts as Pro-oxidant, Excitotoxin, Inflammagen, Immunogen, Mutagen **[27]**.

Pro-oxidant: Al itself is not an oxidant but it is a potent pro-oxidant, which leads to the formation of the Al superoxide radicals promoting the formation of the ROS and LPO **[28]**.

Excitotoxin: Unveiling of brain to Al causes gradual increase in the TNF- α, which is a key cytokine for triggering the release of the glutamate from microglia. Increased concentration of Al in the axonal mitochondria leads to the destruction of mitochondrial functions resulting in dysfunction or damage. This damage leads to the increased sensitivity of the neurons to excitotoxicity and potentiate neuronal damage **[29]**.

Inflammagen: Human sensitivity to Al in a broad spectrum of disorders has been strongly related to inflammatory cascades. Al’s inflammatory activity is possibly mediated by a broad range of methods along with its activity as a pro-oxidant and mediator of countless pro-inflammatory occurrences and biomarkers **[30]**.

Immunogen: Pharmaceutical vaccines contain Al salts as adjuvants and they are also contained in the medications of allergy. Adjuvants boost up the autoimmune responses of inflammatory reactions in the brain. Al is notable for its Immunopotency and enhance immune response **[31]**.

Mutagen: Several experiments disclose that Al influences the DNA damageby production of ROS leading to the alteration of the chromatin structure or by damaging membranes of lysosomes and DNase liberation **[32]**.

6 MANAGEMENTAND TREATMENT

The specific principles in the management of Al neurotoxicity involves:

i) Detecting the origin of Al.
ii) Removal of all causes of Al
iii) Reducing the factors in the person that increase the pathogenicity of Al exposure
iv) Promoting the clearance of Al from the body in a quite secure manner **[33]**.

Basically, estimation of the concentration of Al in body fluids or amount of it in the body may help in providing the better medical care. This is accomplished by decreasing the consumption of High-Al foods and avoiding medicines containing this component. Complexation of Al with those of its complexing agents like fluoride and silicates, the clearance of Al is enhanced **[34]**.

6.1 Chelation Therapy:

Serum Al concentration above 50-60 µg / L (mcg / dL) indicates excess mount of Alwhich correlate with toxicity, and may be used as an indication for symptomatic patients to initiate chelation treatment. In consultation with a nephrologist and a medical toxicologist, Deferoxamine (DFO) chelation treatment should be started and can be carried upon acceptance.DFO, the iron-chelate metal-free ligand extracted from the Streptomyces pilosus bacterium, is used for acute and severe Al toxicity **[35]**.

Neuroprotective Agents for Al Neurotoxicity

Formation of free radicals is responsible for the oxidative damage of neuron; hence it is necessary to examine the antioxidant enzymes which are defensive against the formation the ROS and oxidative damage. Agents that modulate the ROS are probably useful as Neuroprotective agents **[36]**.

Bacopa monnieri extract alleviates the degeneration of neurons in hippocampus, by restricting the superoxide anion formation and a potent cognitive enhancer. It ameliorates the memory impairment by protecting the cholinergic neurons **[37]**.

Carvedilol isknown to haveantioxidant property, it is known to preserve the biological antioxidant system, it is also able to restore the glutathione activity in Al treated rats. Moreover, it is resulted to protection from TNF- *α, and IL-1β* **[38]**.

Hammada scoparia is known to protect the neural cells of the brain in rats by increasing the antioxidant activity of the brain and H. *scoparia* extract is found to restore the altered motor functions to normal by modifying the AChE activity **[39]**.

Curcumin is a natural polyphenolic compound usually found in turmeric. Its structure resembles ubiquinols which is strongly responsible for the antioxidant property. It generally reduces the accumulation of Al in the hippocampal region of brain which is reasonable for the memory formation. It shows the inhibition of LPO induced by iron and increases the glutathione levels **[40]**.

Embillica officinalis is known to reduce the amount of $AlCl_3$ accumulation in the brain. The neuroprotective impact of this plant is proved by inhibiting the AChE activity thereby improving the Acetylcholine (Ach) levels and promoting cognitive events **[41]**.

Cardamom oil consists of 1, 8 cineole of about 31% which inhibits the AChE activity and promotes cognition and proved to possess anti- inflammatory activity. It attenuates the Aβ proteins and leads to decreased neuronal degeneration. It has improvement in the anti-anxiety effect of brain **[42]**.

Moringa oleifera extract decreases the level of serum Al and has enhanced effects on temporal cortex neuro histopathology caused by Al. It is protective against oxidative damage by improving antioxidant enzyme activity and decreasing lipid peroxidation and inhibiting free radical production **[43]**.

Convolvulus pluricaulis prevents Al induced neurotoxicity in the cerebral cortex. It inhibits the oxidative stress and modifies the alerted activity or levels of proteins at cholinergic synapse induced by Al. Combination of CP and rivastigmine tartarate suppressed the increased AChE activity and prevented in decline of Na^+/K^+ATPase **[44]**.

Hesperidin decreased the $AlCl_3$ induced memory loss, cholinergic deficit, Al loading and Aβ anabolism. It also provides neuroprotection of AChE by reducing its activity in the Al treated rats possibly by declining the load of $AlCl_3$ in the hippocampus and cortex of rat brain **[45]**.

Centella asiatica have a demanding role in the fulfilling the free radicals, LPO and sustain the antioxidant enzymes in rat brain areas, thus hindering oxidative stress. It has attenuated the elevated levels of AChE and improves learning and memory performance **[46]**.

7 PREVENTION

The main strategy for preventing the neurotoxicity of Al is to reduce the factors leading exposureof Al. Reduced exposure and absorption of Al, as well as improved endogenous Al clearance, are approaches to minimize and prevent Al concentration and toxicity. Some of the ways to prevent increased exposure to aluminium are:

By avoiding the intake of antacids containing Al and vaccines containing Al salts as the adjuvants. By reduction of use of Al cookware's and food enclosed in Al foils are the few prime factors to be considered to prevent the neurotoxicity **[47]** .

Preparation of aluminium source information and framing awareness of exposure to the foods containing Al like beverages, medications, vaccines, antiperspirants, cosmetics, Al cook ware and drinking water.

Initiating interventions on public health, particularly for vulnerable individuals.

Engage students in studies and research on aluminium toxicity.

Infants formulas have increased amount of Al in the medications so that the parenteral solutions given to the infants are examined.

Studies prove that Silicone (Si) has the ability to reduce the absorption of Al in the GIT and enhances the excretion **[48]**.

8 CONCLUSION

Neurotoxicity arises from a variety of neurological disorders that constitutes the functions of the nervous system. The significant pathways through which Al is known to have a biochemical impact are bio diversely accessible and are known to produce impacts as Pro-oxidant, Excitotoxin, Inflammagen, Immunogen, Mutagen. The systemic activities of Al are undefined and all observed effects on humans are harmful to brain and contribute to subclinical damage. The role of Al in neurotoxicity has been recognized and their molecular mechanism involving in neuronal death has been discussed. Formation of free radicals is responsible for the oxidative damage of neuron hence it is necessary to examine the antioxidant enzymes which are defensive against the formation the ROS and oxidative damage. Agents that modulate the ROS are probably useful as Neuroprotective agents. Still and all the factors that causing neurotoxicity is insufficient and requires compatible evidence.

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