Review Article

Is aluminum exposure a risk factor for neurological disorders?

Elif Inan-Eroglu, Aylin Ayaz
Department of Nutrition and Dietetics, Faculty of Health Sciences, Hacettepe University, Ankara, Turkey

Aluminum (Al) is widely found in the nature. Although the relation between Al and neurodegenerative diseases is still controversial, Al is related with many brain diseases including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Al exposure occurs mainly through environment, occupational, and dietary factors for humans. Al exposure with diet can be through foods, food additives, water, and contamination of Al equipment/utensils. The aim of this review is to summarize various hypotheses, which link Al and neurodegeneration, and to determine the roles of Al exposure through different sources including diet, environment, and occupation. Future studies should be done in vulnerable subgroups of population including children, patients receiving antacid or Al-containing pharmeteucials on a daily basis, patients with reduced renal function, and patients on parenteral nutrition regimens that are likely to be affected by possible adverse health effects of Al. In addition, gender, age, and Al interactions need to be determined. One of the most important challanges in future epidemiological studies is to determine which variables should be controlled. In addition, experimental studies should be more focused and translational. In this context, exposure dose, dose–response effects, and time lapse between exposures and cognitive assessments are very important.

Key words: Aluminum, Alzheimer's disease, multiple sclerosis, neurodegenerative diseases, Parkinson's disease

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INTRODUCTION

Aluminum (Al), the third most commonly found element in the nature after oxygen and silicon, composes nearly 8% of the earth crust. Although Al is found commonly in the environment, there is no known essential role of Al in the living systems. In general, Al is not essential for the growth, reproduction, and sustainability of life in terms of humans and animals.[1] Al is widely used in the fields of medicine, pharmacy, food technology, and cosmetics. Al is also commonly used in food preparation equipment and kitchen utensils.[2] Al exposure occurs mainly through environment, occupational, and diet for humans. Al exposure with diet can be through foods, food additives, water, and contamination of Al equipment/utensils.[1] Although the total intake of Al considerably varies upon country, place of residence, and diet composition, nearly 10 mg of Al is taken to the human body on a daily basis; 9.6 mg of this amount is taken from foods, 0.1–0.4 mg of this amount is taken from kitchen utensils and packaging, and 5 μg of this amount is taken from air.[3] Al absorption is generally less than Al intake, and approximately 95% of the total Al is excreted through feces. Indeed, Al absorption may vary from 0.01% to 1% of the total Al intake.[4,5] It has been reported that citrate may increase Al absorption if it is present in enough amount in the gastrointestinal tract to compete with other binding ligands for Al.[6] Other short-chain carboxylic acids such as acetate, oxalate, lactate, malate, tartrate, gluconate, ascorbate, and carbonate have also been shown to increase Al absorption in some animal studies, although not as effective as citrate.[7-11] This may be due to formation of more stable complex between Al and citrate than other ligands.[12] Contrary to this, it has been reported that the increased diet intake of the compounds containing silicone decreases the absorption of Al and facilitates the excretion of Al.[12] In addition to this, flouride has also been shown to be capable of elimination of

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Address for correspondence: Dr. Aylin Ayaz, Department of Nutrition and Dietetics, Faculty of Health Sciences, Hacettepe University, Ankara 06100, Turkey. E-mail: baylin@hacettepe.edu.tr
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Al in urine and feces.[6] Iron affects the absorption of Al and the accumulation of Al in the brain. Therefore, it has been shown that Al absorption is generally higher at low iron levels. Adequate iron stores may help to reduce the intestinal absorption of Al since iron may compete with Al to bind to the transferrin. The calcium status, like iron, also affects the absorption and accumulation of Al. In animal studies, calcium deficiency in the diet has been shown to increase the rate and amount of Al absorption.[13,14] Vitamin D supplementation may increase Al content in the muscles and hearts. Besides, the parathyroid hormone can increase the absorption of Al by situmilating renal synthesis of 1,25-dihydroxyvitamin D3.[15] Hence, Al bioavailability is highly dependent on individual differences. The necessity of controlling these differences in both experimental and epidemiological studies as confounding variables should be considered.[16] The total body load of Al is approximately 30–50 mg. Only 1% of the total body Al accumulates in the brain.[17,18] Although brain is an important organ that accumulates Al in terms of exposure, it contains less Al than other tissues.[12,18] The gray matter of the brain contains twice as much Al as white matter.[19] In addition to this, it is also reported that Al accumulates in human brains with increasing age.[20,21] Although the mechanisms of how Al enters the brain are not fully known, it is thought that Al passes through the blood–brain barrier through transferrin and accumulates in the area of the brain cortex that is rich in transferrin receptors.[17,22]

Although there is lots of evidence implicating that Al in the progression of events leads to neurodegenerative diseases, some of the evidence remains controversial. However, it is widely accepted that Al is a recognized neurotoxin, which could cause neurodegeneration.[23] Al affects >200 important biological reactions and causes negative effects on central nervous system. Among these reactions affected by Al, there are mechanisms effective on brain development, such as axonal transport, neurotransmitter synthesis, synaptic transmission, phosphorylation or de-phosphorylation of proteins, protein degradation, gene expression, peroxidation, and inflammatory responses.[24] Al can bind to histone-DNA complex and induce conformational changes of chromatin and induce topological changes of DNA.[25,26] Al can also alter gene expression by inducing decreased expression of neurofilament and tubulin, altered expression of genes of neurofilament, amyloid precursor protein (APP), and neuron-specific enolase, decreased expression of transferrin receptor, altered expression of RNA polymerase I, altered expression of oxidative stress marker genes (SOD1, glutathione reductase, etc.), and altered expression of β-APP secretase.[27-32] In addition to these effects of Al, it has been suggested that Al can affect cellular functions such as inhibiting the activity of hexokinase, phosphofructokinase, and glucose-6-phosphate dehydrogenase and causing mitochondrial dysfunction and depletion of adenine-triphosphate (ATP).[33-37] The aforementioned phosphorylation or de-phosphorylation reactions that can be affected by Al are inhibiting the activity of protein phosphatase and dephosphorylation of tau, increasing the activity of protein kinase C and cytoskeleton proteins, and inducing nonenzymatic phosphorylation of tau.[38-41] Al can also cause an abnormal accumulation of proteins by causing the accumulation of tau protein in neuroblastoma cells, neurofibrillary degeneration *in vivo*, and the accumulation of amyloid β protein (AβP) *in vivo*.[42-45]

While *in vivo* and *in vitro* studies have shown that Al has negative effects on the central nervous system, the results are conflicting. Studies in Al welders found that Al may cause memory and attention task deficits, but on the other hand, there are studies which showed that occupational Al exposure does not lead to a cognitive or motor performance decline.[46-49] In addition to this occupational Al exposure studies, cognitive deficit was demonstrated in the studies that were made with dialysis patients after administration of the Al chelator.[50,51] On the contrary, Jackson *et al*.[52] reported no significant differences on cognitive tests in dialysis patients. These studies show that more studies have to be done for determining the relationship between Al and neurological disorders. Although the relation between Al and neurodegenerative diseases is still controversial, Al is related with many brain diseases including Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS) [Figure 1].[24,53-56]

In light of these information, the aim of this review is to summarize various hypotheses, which link Al and neurodegeneration, and to determine the roles of Al exposure through different sources including diet, environment, and occupation.

Aluminum and neurological disorders

Alzheimer's disease

AD is characterized by a neurological progressive impairment affecting several cognitive domains, behavior, and personality.[57] AD is accompanied by changes in cerebral functions as a result of biochemical incidents, each of which is related with each other. These cerebral dysfunctions result in difficulties in receiving/processing new information, difficulties in doing previously known activities/works, confusion, not participating in social activities, loss of memory, and personality changes.[58] Typical neuropathological signs of the disease are intracellular neurofibrillary tangles (hyper phosphorylation of tau protein), deposition of extracellular senile plaques (hyper phosphorylation of AβP, optimal losses of synapses and neurons in hippocampal and cerebral cortical regions, cortical and subcortical atrophy, and cerebrovascular amyloids.[54,59,60] Early-onset AD is related to familial gene mutations, which results in increased

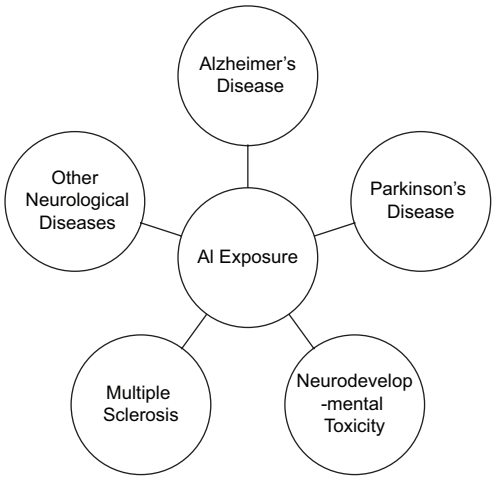

Figure 1: Summary of neurotoxicity of aluminum

secretion of neurotoxic AβP. Apolipoprotein E susceptibility gene is a risk factor in AD. The late-onset AD, detected in 85%–95% of the cases of AD, is not related with any gene mutation.[61]

The etiological factors of AD are not exactly known. However, it is thought that genetic factors, oxidative stress, infectious factors, and environmental factors are playing role in AD.[60] As there is no sufficient genetic information about AD, it is thought that environmental factors interact with other factors and provide a basis for the formation of this disease. Al is one of these environmental factors.[62] The hypothesis, stating that Al was one of the environmental factors in the pathogenesis of AD, was named as "Al hypothesis," based on various neuro-toxicological, analytical, and epidemiological data found in the 1960s.[63-65] The beginning of the hypothesis, stating that Al was included in the etiology of AD, is revealed by observing the neurofibrillary degeneration after the intracerebral injection of Al into rabbit's brain.[63] The increasing Al levels were reported in 1973 in postmortem brain samples of people with AD and they were related with AD.[64]

The role of Al in AD was related to different incidents, independent from each other. These are as follows:

1. High concentrations of Al increase amyloid aggregation and deposition, the main feature of the neuropathology of AD[66]
2. *In vitro* and *in vivo*, by means of pro-inflammatory transcription factor nuclear factor-kappa B (NF-kB), Al increases the inflammatory signalization, one of the main features of the brain with AD[20,67]
3. Al-induced mRNAs and microRNAs (miRNAs) show similarity with mRNAs and miRNAs[68]
4. In transgenic animal models with AD, dietary Al increases the formation of pathological determinants such as lipid peroxidation, oxidative stress, apoptosis, and gene expression deficiencies[44,69,70]
5. The disorders observed in AD such as chromatin compression, impaired energy usage, and impaired signalization including chemical messengers such as ATP were also detected in cells exposed to Al or in animal models with AD[71,72]
6. In the studies, the amount of Al in water was related to the incidence of AD.[20,73,74]

Although Al is not known to be neurotoxin, there is still no consensus on the relationship between Al and AD, the results from different studies are not consistent.[7] Some studies show that aluminum promotes precursor expression of the AβP, increases the levels of the B-40 and B-42 fragments in the brain, and boosts the aggregation of the AβP,[44,75,76] whereas the results previously obtained for the Aβ pathways cannot be reproduced *in vivo*.[77,78] Although experimental studies have produced inconsistent results on the relationship between Al and AD, epidemiological studies provide important consistent results. A recent meta-analysis by Wang *et al*.[57] examined 8 epidemiological studies to determine exposure to Al and association with AD. A significant correlation was found between Al exposure and AD risk according to the meta-analysis of cohort studies in which a total of 10,567 individuals were included and exposed to Al from drinking water and occupational exposure, with follow-up times ranging from 8 to 48 years. McLachlan *et al*.[79] found a dose–response correlation between an increasing concentration of Al in the drinking water (100 mg/L or greater Al) and a higher risk of developing AD. There are several epidemiological studies of drinking water and AD risk that have also shown dose–response effects.[73,80]

Parkinson's disease

PD, the widely observed neurodegenerative disorder after AD, is characterized with selective death of neurons in substantia nigra. By leading genetic and/or acquired disorders in ubiquitin-proteasome system, it can cause the deposition of ubiquitin-added proteins and neuronal deaths.[81] It has been suggested that several molecular mechanisms including mitochondrial dysfunction, impairment of protein quality pathways, oxidative/nitrative stress, microglia activation, and inflammation are responsible for neuronal death in PD pathogenesis.[82,83] In addition to the neuronal loss, the other neuropathological hallmark of PD is the presence of Lewy bodies in the surviving neurons. These neurons are eosinophilic cytoplasmic inclusions containing aggregates of protein such as α-synuclein (α-syn).[81]

PD is a neurodegenerative disorder, affecting speaking and motor abilities of the patient, which is characterized with tremors in the face, hands and jaw, muscle rigidity, and slow physical activities. PD occurs as a result of the decrease of

stimuli by basal ganglia in motor cortex, depending on the death of neurons in globus pallidus and substantia nigra, which normally synthesizes and releases epinephrine and dopamine.[81] PD can progress with head injuries/traumas, encephalitic virus, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, contaminant including drugs such as heroin) and exposure to some pesticides.[81] As Al^{+3} toxicity causes AD-type dementia in some patients with PD, it is thought that Al is playing a role in PD.[81] Moreover, catecholamine neurotransmitters and catechol parts of epinephrine and dopamine are important binding parts of Al^{+3}. Although epinephrine and dopamine are weak Mg^{+2} binders in millimolar levels, they bind Al^{+3} in nanomolar levels. It was detected that there were high Al^{+3} and Fe^{+3} levels indicating the death of neurons in neuromelanin granules and Lewy bodies of substantia nigra and locus coeruleus (the blue part of brain stem in which there are neurons including neuro-epinephrine) parts in the brains of patients with PD.[84] As a result of iron metabolism impaired by Al^{+3}, high levels of iron accumulate in the neurons of patients with PD, but there is no increase observed in the levels of ferritin. Consequently, oxidative damage occurs, which causes neural deaths in substantia nigra and other parts of the brain affected from PD.[84]

The relationship between PD and Al has also been demonstrated in gastric ulcer patients due to the use of Al-containing antacids.[85] Another indirect evidence between Al and PD is the ability of Al to activate the monoamine oxidase B. This enzyme increases with age and PD.[86] In addition, monoamine oxidase B may promote α-syn fibril formation.[87] It is suggested that this situation may explain the relationship between neurotoxic metals and PD.[88] Activation of the NF-kB transcription factor and triggering of inflammatory processes have been found to occur synergistically after simultaneous treatment of experimental animals with a dopaminergic neurotoxin, MPTP, and low-level Al in drinking water.[22] Yasui *et al*.[89] found that Al concentration in the substantia nigra, caudate nucleus, and globus pallidus was higher in PD brains and significantly higher in gray matter and the basal ganglia. In parallel, Good *et al*.[90] found increased Al levels in the neuromelanin granules of two of three PD cases.

Multiple sclerosis

MS is a chronic, immune-mediated, and demyelinating disease of the central nervous system, the etiology of which has not been known yet. Iron concentrations in urine were found high in secondary progressive, recurrent, and recovering patients with MS.[53] Moreover, it was detected that Al concentrations in the urine of these patients also increased. The Al excretion levels of these patients were found same as the individuals who got metal chelation therapy. Increased iron concentrations in the urine show impaired iron metabolism in patients with MS. Al excretion levels also resemble Al intoxication. This situation indicates that Al can be an environmental factor in MS etiology.[53] In addition, use of Al adjuvant-containing vaccines has also been associated with increased incidence of MS.[91,92]

Dialysis encephalopathy

For individuals with chronic kidney disease, there is a bilateral risk associated with Al. First, these patients are exposed to Al as part of the treatment process, and second, their ability to excrete Al from the body is reduced because of the disease.[93] Chronic kidney disease patients also have difficulty to excrete phosphate from the body. The high blood phosphate levels of these patients increase the risk of death from bone and heart diseases. Al hydroxide began to be used as a phosphate binder in patients with chronic kidney disease to limit phosphate absorption in the 1960s.[93] The use of Al-containing phosphate binders, especially with alkalinizing citrate solution (Shohl's solution), has been found to be more risky to form Al citrate complex which consequently increase the absorption of Al.[94,95] Dialysis encephalopathy, first described in 1972, has emerged as a complication of prolonged hemodialysis exposure.[96] Patients with dialysis encephalopathy have difficulty in speaking (dysarthria), movement planning disorder (dyspraxia), unconsciousness and psychosis following ataxia, personality changes, myoclonic movements, electroencephalographic abnormalities, convulsions, and dementia.[93]

The mechanisms of dialysis encephalopathy are not exactly known. Al passes through the blood–brain barrier through the transferrin and accumulates in the area of the brain cortex that is rich in transferrin receptors. This region where the distribution of pyramidal neurons is made requires a high degree of Fe for the synthesis of respiratory chain enzymes. The damage in this area is thought to have resulted in neuropathy.[97]

It was found that Al levels in brain, muscle, and other tissues of dialysis encephalopathy patients were high. Serum Al levels >80 μg/L have been associated with dialysis encephalopathy.[98] In addition, cerebral cortical Al concentrations of patients with dialysis encephalopathy were reported as 10–25 μg/g dry brain weight.[97] The Al content of the dialysis fluids used in many cases with encephalopathy was determined to be >200 μg/L.[99] Nowadays, the exposure of dialysis patients to Al is the minimum, as the Al level of dialysis fluid in the majority of dialysis centers is <10 μg/L.[100]

Aluminum exposure with diet

Exposure to Al in humans is mainly through diet. Al exposure to the diet can be through contamination of foods,

food additives, water, and Al kitchenwares.[1] The amount of Al in foods differs according to their Al content or the interaction of nutrients with the Al kitchenwares in the process of storage, preparation, and cooking of foods.[40] Although the amount of Al in the soil is high (3%–10%), many plants contain low amounts of Al.[97] When the pH of the soil is <4.5–5.0, Al is dissolved in water and absorbed by the root of the plant.[101] The amount of Al in animal-derived foods depends on the low amount of Al in animal feed and on the limited availability of Al to animals in animal-derived products such as eggs and milk. As a result, most of the animal-derived foods contain <1 μg/g Al.[97]

Except for foods and additives including Al, Al exposure with diet can increase due to storage of foods in Al containers and Al cookware (pot, pan, tray, coffeepot, etc.) used in food preparation and cooking and contact with folios.[1] Although the amount of Al exposed as a result of the consumption of foods prepared in Al cookware was lower than the amount of Al that was taken from other sources, in case of frequent usage of Al cookware, the Al migration to food from these cookware increased significantly.[1] Moreover, factors such as cooking time and temperature, the composition of food, pH value, and the existence of other substances (organic acids, salt, and other ions) also affect Al migrations to foods. Under normal circumstances, the Al migration from substances contact with the food constitutes a small part of the total dietary exposure. In addition, the use of Al pots, plates, or folios with foods such as apple, tomato, and salted fish increases the Al migrations to these foods. Furthermore, it was reported that the use of Al plates and trays, especially with acidic foods such as tomato, pickle, and vinegar, caused the increase of Al migrations.[1,102] The provisional tolerable weekly intake level of Al was reevaluated by the Joint Expert Committee on Food Additives in 2011 in light of new toxicological studies. According to this evaluation, the provisional tolerable weekly intake level, previously published as 1 mg/kg body weight (BW), was changed as 2 mg/kg BW.[103]

Aluminum exposure from environment

Although Al is found in the earth crust in a large amount, the majority of natural water contain very small amounts of dissolved Al (<10 μg/L) and marine water contain 1 μg/L of Al. Al in marine water generally accumulates in unicellular algae.[97] The development of modern industrial technologies and the spreading of chemicals into the atmosphere may cause acid rains.[104] When natural water acidify due to acid rain or when natural water are treated with Al sulfate to obtain drinking water, the amount of Al in natural water increases.[97] Strong mineral acids such as sulfur and nitrogen oxalic acid in acid rain can cause mobilization of Al by dissolving it from the soil.[97] The amount of acid in lakes and rivers acidified by acid rain can reach up to 700 μg/L. This level is generally regarded as a toxic level for fish.[97] In addition, natural events such as soil erosion, fragmentation of rocks, and volcanic activity result in the removal and redistribution of Al in other environmental components, including water, air, and biota.[102] The Al concentration of air varies between 20 and 500 ng/m^3 in rural areas and 1000 and 6000 ng/m^3 in urban areas. Humans are exposed to environmental alumina at a concentration of 200 ng/m^3 and a particle size of <5 μm. A person with a normal ventilation volume of 20 m^3 is 40 μg of Al breath/day.[99]

Occupational aluminum exposure

With the increasing use of Al in everyday life and industry, Al exposure has become inevitable. Potential Al exposure is expected to be higher in people working in certain occupational groups (such as Al refining and metal industries, printing and publishing, and automotive business).[19]

Occupational exposure to Al particles during the production of Al dusts reached 100 mg/m^3 in the 1950s.[105] However, the exposure levels for Al dust production in the 1990s were reported to be 5–21 mg/m^3 and the exposure levels for the production of Al fuels were reported to be 1–4 mg/m^3.[106] During Al welding process, 0.2–5 mg/m^3 Al is produced. Powder production and welding often lead to occupational Al exposure at high levels. Cognitive deficits, attention deficits, learning and verbal or visual disorders, and "concept formation" problems have been reported in workers exposed to occupational Al exposure.[1]

CONCLUSION

It is well established that Al is a neurotoxic agent. However, the link of Al to the etiology of various serious neurological disorders such as AD remains still unclear. In spite of this uncertainty, a number of epidemiological reports concerning Al exposure and the risks of neurological disorders are available in the scientific literature. An important reason for this uncertainty is the ethical concerns of tests conducted in humans. Thus, many studies have been conducted on animals and animals have been exposed to Al throughout their lives so that the effects of Al can be fully observed in many of these studies. Al exposure should be kept to minimum since the potential effects on human health of Al are not fully understood. Future studies should be done in vulnerable subgroups of population including children, patients receiving antacids or Al-containing pharmeteucials on a daily basis, patients with reduced renal function, and patients on parenteral nutrition regimens that are likely to be affected by possible adverse health effects of Al. In addition, gender, age, and Al interactions need to be determined. One of the most important challanges in future

epidemiological studies is to decide which variables should be controlled. In addition, experimental studies should be more focused and translational. In this context, exposure dose, dose–response effects, and time lapse between exposures and cognitive assessments are very important.

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