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Review

Low levels of aluminum can lead to behavioral and morphological changes associated with Alzheimer's disease and age-related neurodegeneration

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ABSTRACT

Aluminum (Al) is a very common component of the earth's mineral composition. It is not essential element for life and is a constituent of rather inert minerals. Therefore, it has often been regarded as not presenting a significant health hazard. As a result, aluminum-containing agents been used in the preparation of many foodstuffs processing steps and also in elimination of particulate organic matter from water. More recently, the reduced pH of bodies of water resulting from acid rain has led to mobilization of aluminum-containing minerals into a more soluble form, and these have thus entered residential drinking water resources. By this means, the body burden of aluminum in humans has increased. Epidemiological and experimental findings indicate that aluminum is not as harmless as was previously thought, and that aluminum may contribute to the inception and advancement of Alzheimer's disease. Epidemiological data is reinforced by indications that aluminum exposure can result in excess inflammatory activity within the brain. Activation of the immune system not initiated by an infectious agent, typifies the aging brain and is even more augmented in several neurodegenerative diseases. The origin of most age-related neurological disorders is generally not known but as they are largely not of genetic derivation, their development is likely triggered by unknown environmental factors. There is a growing and consistent body of evidence that points to aluminum as being one such significant influence. Evidence is presented that reinforces the likelihood that aluminum is a factor speeding the rate of brain aging. Such acceleration would inevitably enlarge the incidence of age-related neurological diseases.

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1. Aluminum in the Environment

Aluminum (Al) is the third most abundant element in the earth's crust (Priest et al., 1988). It was only in 1825 that this metal was isolated in its elemental metallic form by the Danish physicist Hans Oersted (Sigel and Sigel, 1988). Al products have many modern applications. Adding aluminum sulfate and lime to water causes aluminum hydroxide formation, which leads to coagulation of pollutants. This procedure is used widely for water clarification in reservoirs. Al-containing materials are also commonly found in foods. These include emulsifying agents in processed cheese, firming agents in pickles, baking powder, and several food colorings. These aluminum-based colors also have cosmetic applications. Infant formulae can have a significant aluminum content (Dabeka et al., 2011; Burrell and Exley, 2010). Concentrations as high as 1.8 mM Al can be reached in the fruit juice resulting when acidic fruit is boiled in aluminum cookware (Fimreite et al., 1997). Drinking water has variable Al content. Several cities have reported concentrations as high as 0.4–1 mg/L of aluminum in their water. Although the health effects of aluminum on humans are not definitive, the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives lowered the allowable intake of aluminum in 2006 – from 7 mg/kg body weight to 1 mg/kg body weight per week. That is equivalent to 63 mg of aluminum per week for a 140-pound adult. The average commercial muffin alone has been reported to contain 28 mg of aluminum.

Many medicines contain Al salts, notably aluminum oxide is used as an effective adjuvant in vaccines in order to promote immune activation. Antiperspirants, buffered aspirin and antacids commonly contain Al (300–600 mg/tablet).

The most common form of human exposure to Al is by way of the gastrointestinal tract. The rate of absorption here is around 0.2% (Priest et al., 1988). Once Al salts are transferred to the vascular system in the blood, most of the metal is bound to transferrin (Harris et al., 2003). Al^{3+} can enter the nervous system by transport across the blood–brain barrier using receptor-mediated endocytosis of transferrin. Approximately 0.005% of the aluminum-protein complexes enter the brain by this means (Yokel et al., 2001).

Al in the environment was originally considered to be innocuous, because Al salts form monomeric hydroxy compounds in water which start to form increasingly high molecular weight complexes as the solution ages. Because of the formation of these colloidal insoluble Al species, its absorption was thought to be restricted. However, Al compounds are known to be toxic to both plants (Kochian and Jones, 1997) and animals (Sparling and Campbell, 1997) and there has been an increased disquiet concerning the metal's potentially adverse effects on human health (LaZerte et al., 1997). While concerns about Al toxicity to humans have been expressed for over 80 years, the medical establishment has continuously tended to discount them. For example an article in the Journal of the American Medical Association in 1935 stated, "Propaganda as to possible dangers resulting from the use of aluminum cooking vessels is so persistent that one suspects ulterior motives in its background" (Monier-Williams, 1935).

The increasing prevalence of acid rain as a result of fossil fuel combustion can lead to the liberation of larger amounts of Al salts from insoluble minerals, resulting in greater bioavailability (Smith, 1996).

2. Transitory exposure to high levels of aluminum can result in neurological disturbance

The possibility of Al salts constituting a risk factor in enhancing the likelihood of neurological disease has been originally raised by a number of clinical studies. Thus, hemodialysis of patients with severe kidney disease has led to toxic levels of Al in the blood, from exposure to aluminum in dialysis fluid and from the administration of high levels of aluminum-containing phosphate binders among patients who cannot excrete it. The resulting aluminum-induced dialysis encephalopathy following hemodialysis is accompanied by elevated levels of Al in the brain (Russo et al., 1992) and ingestion of Al salts can lead to the deposition of insoluble Al-containing materials within the brain (Bowdler et al., 1979). Clinical status is improved by therapeutic use of an Al chelator, desferrioxamine (Erasmus et al., 1995). Blood concentrations of Al as high as 7 μM, have been found in dialysis patients even in the absence of overt dementia (Altmann et al., 1987). Aluminum-induced encephalopathy also occurs in patients with kidney failure, treated with bladder irrigation using 1% alum (Phelps et al., 1999). A form of encephalopathy has been reported in workers in the aluminum industry, and this is characterized by intellectual deficits, loss of muscle control, tremor and spinocerebellar degeneration (Polizzi et al., 2002). A typical report concerns a chronic renal failure patient, who was treated phosphate-binding Al-hydroxy gels for a prolonged period. And then developed Al-induced encephalopathy nine months prior to death. Post-mortem neuropathology showed pronounced proliferation of microglia and astrocytes in specific brain areas (Shirabe et al., 2002).

Abnormal neurological signs have also been seen in some patients receiving intramuscular injections of Al-containing vaccines (Couette et al., 2009). In consequence, the World Health Organization (WHO) Vaccine Safety Advisory Committee has recognized that there may be a subset of predisposed individuals who may be sensitive to Al adjuvants (Authier et al., 2001). Overall, there is good evidence that high levels of aluminum exposure can have adverse effects on human health.

In the past, inhalation of Al in the form of the powdered oxide was used as a prophylactic agent against silicotic lung disease of miners (Crombie et al., 1944). The procedure was described as beneficial in an animal model of silicosis (Dubois et al., 1988) and continued despite the conclusion that humans suffering from silicosis, did not appreciably benefit from Al treatment (Kennedy, 1956). Harmful effects of inhaled Al, especially upon brain function, were later described (Rifat et al., 1990). More recently, a major accidental exposure of a rather large population to excessive amounts of Al occurred in Camelford, U. K. caused by the accidental release of large amounts of Al sulfate into a nearby reservoir. The neurological consequences from this mishap are being studied and there is already evidence of harmful effects on neurological function in some of the exposed population (Altmann et al., 1999). Pathological examination of the brain a person who was exposed to Al at Camelford and later died of an undetermined neurological condition, disclosed early-onset beta amyloid angiopathy in the cerebral cortical and leptomeningeal blood vessels. High Al concentrations were also present in the more seriously affected regions of the cortex (Exley and Esiri, 2006).

Correlative changes are never sufficient to irrefutably demonstrate causation and it has been suggested that that Al entry into the brain consequent to damage to the blood–brain barrier as a secondary event. However, dialysis encephalopathy can be treated with some success using the trivalent metal chelator desferrioxamine. This indicated that Al is directly neurotoxic (McLachlan et al., 1991). These results have not been followed up in recent years, perhaps partly due to the unfavorable side effects of desferrioxamine treatment that include muscle pain, nausea, and erythema and visual deficits. There may be a lack of interest by pharmaceutical companies in a promotion of a drug that is not patentable. Treatment of aluminum-related bone disease using desferrioxamine can mobilize Al from deposits in bone, has been reported to lead to elevated serum Al and to the appearance of