Chapter 6
Exposure to Aluminum in Daily Life and Alzheimer's Disease

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Abstract Aluminum is the third most abundant element on the earth's crust and has been considered a constituent of rather inert minerals. Therefore, it has often been regarded as not having a significant health hazard. Consequently, aluminum-containing agents have been used in processing, packaging, and storage of food products and also in the treatment of drinking water as flocculants. Recently, acid rain due to environmental pollution has transported more aluminum-containing minerals into residential drinking water resources. It is therefore not surprising that aluminum burden in the human body has increased. Research data showed that aluminum is not as safe as was previously thought and that aluminum may contribute to the initial advancement of Alzheimer's disease. Aluminum-mediated neurodegeneration resulting in cognitive dysfunction has been associated with amyloidβ (Aβ) deposition, formation of intraneuronal neurofibrillary tangles (NFTs), and apoptotic neuronal death characterized histopathologically in AD. The origin of Alzheimer's disease is generally not known; its development is likely triggered by unknown environmental factors. Although it is inconsistent with the link between human exposure to aluminum in everyday life and its contribution to Alzheimer's disease, a growing body of evidence points to aluminum as being one such significant influence.

Keywords Aluminum · Daily life exposure · Alzheimer's disease

6.1 Introduction

Aluminum (Al) is very abundant on the earth. Al-containing materials have long been extensively used in food additives, water purification, medications, Al-adjuvanted vaccines, and many other products [3]. The reduced pH of bodies of water due to acid rain has transported more aluminum-containing minerals into various environmental media. Thus, human body is readily exposed to a significant

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amount of Al in our daily life. New evidence showed that brain Al concentration can reach 0.35 mg/kg, about 100 times over plasma concentration [1]. This selective accumulation has been raising concern over the aluminum's potential adverse effects in neurotoxicity and neurodegeneration. Alzheimer's disease (AD) is a progressive neurodegenerative cerebral disorder. Al-mediated neurodegeneration resulting in cognitive dysfunction has been associated with amyloid**β** (A**β**) deposition, formation of intraneuronal neurofibrillary tangles (NFTs), and apoptotic neuronal death characterized histopathologically in AD [19]. Although the associations between Al exposure in daily life and AD are not consistent, many studies support Al exposure is a risk factor for the pathogenesis of AD.

6.2 Natural Sources of Aluminum Exposure

Aluminum (Al) is the third most abundant element on the earth's crust with 7.5% where it is frequently found as aluminosilicates, hydroxides, phosphates, sulfates, and cryolite. Soils and weathered rocks constitute the major sources of aluminum in environmental media. The transform and transport of aluminum is marked effected by environmental factors such as pH, salinity, and the presence of various species with which it may form complexes. In general, the solubility and mobility of aluminum in soil is not only dependent on soil content of organic matter capable of forming aluminum-organic complexes but also low pH such as in areas prone to acid rain or in acidic mine tailings. Natural processes account for most of the redistribution of aluminum in the environment. Aluminum is also released due to anthropogenic activities such as mining and industrial uses, in the production of aluminum metal and other aluminum compounds [6].

Aluminum levels in environmental media vary widely depending upon the location and sampling site. In general, the concentration in soils varies widely, ranging from about 7 to over 100 g/kg. Background levels of aluminum in the atmosphere are low, typically ranging from about 0.005 to 0.18 μg/m^3 [13]. However, reports showed higher Al levels were seen in urban and industrial locations. Nowadays Al concentration in surface water is generally lower than 0.1 mg/L; however, when PH in water is decreased, the level of aluminum increases due to the increased solubility of aluminum compounds [13].

6.3 Anthropogenic Sources of Aluminum Exposure

In 1825 aluminum was isolated in its elemental form by the Danish physicist Hans Oersted. Due to its excellent material properties such as castability in any shape, plasticity, heat conduction, low density, low melting point, oxidative passivation, and suppleness with concurrent toughness, aluminum metal and its alloys have many modern applications, especially in transportation, building and construction,

packaging, and electrical equipment. Aluminum powders are used in pigments and paints, fuel additives, explosives, and propellants. Aluminum oxides are used as food additives and in the manufacture. Aluminum hydroxide is used widely in pharmaceutical and personal care products. Food-related uses of aluminum compounds include preservatives, fillers, coloring agents, anticaking agents, emulsifiers, and baking powders; soy-based infant formula can contain aluminum. Natural aluminum minerals especially bentonite and zeolite are used in water purification, sugar refining, brewing, and paper industries. Currently, the use of aluminum makes us live in the aluminum age ensuring an accelerated exposure to aluminum in our daily lives and a burgeoning body burden of aluminum for each and every one of us [3].

6.4 Aluminum Exposures of General Population in Daily Life

The general population is primarily exposed to aluminum through the consumption of food items [26]. Aluminum in drinking water represents another, minor, source of exposure. Additional exposures may arise from the use of aluminum compounds in pharmaceuticals and consumer products. Uptake through inhalation is negligible for the general public, although workers who are exposed to higher Al dust in their workplace have an increased tendency to contract pulmonary aluminosis (restrictive lung disease).

Under normal conditions, it is clear that aluminum concentration is relatively low in most unprocessed foods. Mean fresh weight concentrations (in μg/g) in common food types are shown below: beverages (1.5); fruit (2.7); fish (fresh or tinned, 3.2); milk and dairy products (4.5); meat, sausage, and offal (5.4); vegetables (5.7); sugar and sugar-rich products (6.7); bread, cake, and pastries (7.4); and edible seeds (beans, peas, etc., 9.3) [13]; it is well known that there are big differences in the aluminum content of the individual food types between and within various countries. Many reports have estimated Al dietary exposure in different countries and regions, such as the United States, Greece, Belgium, South China, and the European Union. These data show large variations.

In general, human exposure to aluminum from food contact materials is negligible. However, the use of aluminum household utensils for acidic or salted foods, such as apple puree, rhubarb, tomato puree, or salted herring, could result in an additional aluminum exposure due to the increased solubility of aluminum. Also, the use of aluminum bottles for acidic beverages such as apple juice with mineral water or tea might moderately increase the aluminum exposure. High aluminum levels in food were also seen in convenience stores and fast-food restaurants especially those that contain tomato, different types of pickles, and vinegar when using aluminum vessels and trays [30].

Total dietary aluminum exposure from all sources has been estimated in a number of European countries (Netherlands, Hungary, Germany, Sweden, and Italy). Cereals and cereal products, vegetables, and beverages accounted for 10% more of

the dietary aluminum exposure in the general population. Mean dietary exposure from water and food in nonoccupational exposed adults ranged from 1.6 to 13 mg aluminum per day. This amount corresponds to an exposure of 0.2–1.5 mg/kg body weight (bw) per week for a 60 kg adult [13]. It must be noted that there are large variations in the average contamination between the different countries and, within a country, between different surveys. And large aluminum variations in individual exposure can occur for differences in living environment, soil contamination, dietary habits, or the consumption of foods with aluminum additives [26].

Due to higher food intake than adults, children may be the highest potential exposure group when expressed as aluminum per kg body weight. The estimated aluminum exposure at the 97.5 percentile in children aged 3–15 years was 0.7 mg/kg bw/week in France and that for toddlers (1.5–4.5 years) was 2.3 mg/kg bw/week and that for those aged 4–18 years was 1.7 mg/kg bw/week in the United Kingdom. And the potential estimated exposure for infants aged 0–3, 4–6, 7–9, and 10–12 months were 0.10, 0.20, 0.43, and 0.78 mg/kg bw/week, respectively. The mean potential exposure to aluminum in 3-month-old infants from a variety of infant formulae was up to 0.6 mg/kg bw/week for milk-based formulae and was 0.75 mg/kg bw/week for soya-based formulae.

6.5 Absorption, Distribution, and Excretion of Aluminum

Although consumption of food items comprises the primary source of aluminum for the general population, studies in humans and experimental animals show that the oral bioavailability of aluminum from drinking water is about 0.3%, whereas the bioavailability of aluminum from food and beverages is about 0.1%. Aluminum chemical forms and ligands in dietary constituents contribute to the bioavailability of aluminum. At least tenfold variation was found in the oral absorption of aluminum from food depending on the chemical forms present in the intestinal tract. Ligands in food can either enhance the uptake by forming water-soluble complexes (e.g., with carboxylic acids such as citric and lactic acids) or reduce it by forming insoluble compounds (e.g., with phosphate, dissolved silicate, phytate, or polyphenols) [13].

After absorption, aluminum distribution is unequal in all tissues in humans, and there is accumulation in some tissues. The total aluminum is in the range of 30–50 mg/kg bw in healthy human subjects. Normal serum aluminum concentrations are about 1–3 μg/L. In the human body, approximately one-half of the aluminum accumulates in the skeleton, and approximately one-fourth accumulates in the lungs (from accumulation of inhaled insoluble aluminum compounds). Aluminum level in human skeleton is in the range of 5–10 mg/kg. Aluminum also exits in the human skin, lower gastrointestinal tract, lymph nodes, adrenals, parathyroid glands, and most soft tissue organs. In rats higher aluminum levels were found in the spleen, liver, bone, and kidneys than in the brain, muscle, heart, or lung. Moreover, aluminum can cross the placenta and distribute into the developing fetus and even

distribute to the milk of lactating mothers. Available studies indicate that aluminum levels increase with aging in a number of tissues and organs (bone, muscle, lung, liver, and kidney) of experimental animals.

Aluminum excretion via the kidneys constitutes a primary route. And aluminum is excreted minorly by the bile. Unabsorbed aluminum is eliminated through alimentary tract in the feces. It takes a very long time for various organs and tissues of experimental animals and humans to eliminate aluminum. There are big differences in the elimination half-life of aluminum, ranging from hours, days, and months to years, suggesting that there is more than one compartment of aluminum storage from which aluminum is eliminated. Although aluminum persists longer time in humans than in rodents, there is little information on allometric scaling of aluminum elimination rates that can be used to extrapolate these results from rodent to the human.

Al in the environment was originally considered harmless, because aluminum exists in only one oxidation state (+3) and does not undergo oxidation reduction reactions, and in solution, Al^{3+} salts form monomeric hydroxy compounds which start to form polymeric and colloidal particles as the solution ages. Because of the formation of these insoluble aluminum species, it was assumed that absorption would be limited and thus the metal would be innocuous [4]. However, 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. New evidence showed that brain Al concentration can reach 100 times over plasma concentration. This selective accumulation may result from major bioconcentration by the cerebral vasculature [1]. The ensuing content of Al in the brain is within molarity range of 4–15 mM. This is over ten times the concentration of Al that is toxic to isolated human neuronal and glial cells. For this reason, there has been a rising concern over the aluminum's potential adverse health effects. In 2007, the provisional tolerable weekly intake (PTWI) of aluminum was reduced from7.0 mg per kg body weight to 1.0 mg per kg body weight because of the adverse effects of aluminum on the reproductive and nervous system in experimental animals. However, in 2011, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) revised the PTWI to 2.0 mg per kg body weight as a result of new bioavailability and toxicological data.

6.6 Aluminum-Induced Neurotoxicity and Aluminum Hypothesis in Etiology of AD

Aluminum has no any definite biological function, suggesting that the element possesses properties which are neutral or incompatible with fundamental life processes. Aluminum as a neurotoxic metal was initially established in the early 1970s after years of uncertainty. Studies in vitro and in vivo have clearly established the potential of aluminum to cause significant neurotoxicity and neurodegeneration. However,

in humans, the proposed connection between aluminum exposure and neurotoxicity was established as a result of studies of dementia in patients undergoing long-term dialysis chronically exposed parenterally to high concentrations of aluminum, first linking Alzheimer's disease (AD) to aluminum exposure. AD is a progressive mental deterioration manifested by memory loss, inability to calculate, visual spatial disturbances, confusion, and disorientation. The neuropathological characteristics include formation of intraneuronal neurofibrillary tangles (NFTs), deposition of amyloid beta peptide (Aβ) in neuritic plaques or senile plaques (SPs), loss of neurons, and synapses in the cerebral cortex and certain subcortical regions. The causes for AD are still mostly unknown, although unproven etiological factors have included genetics, head trauma, oxidative stress, infectious agents, and environmental factors including aluminum toxicity. AD has decades-long prodromal phase, suggesting that there may exist slow but progressive accumulation of a toxic or infective agent over time. Such potential environmental agents are slowly increased in susceptible neural cell types of AD-vulnerable brain regions to adverse levels till old age, giving rise to AD neuropathology without rapid neuronal lysis. Chronic aluminum neurotoxicity best matches this profile [2, 12].

The Aluminum Hypothesis, the idea that aluminum exposure is a causal factor in promoting Alzheimer's disease, dates back to 1965 when administration of aluminum salts into the brains of rabbits induced cognitive deficits in association with the formation of neurofibrillary changes that, after silver staining, seemed similar to the neurofibrillary tangles which exists in the brains of AD cases. Crapper et al. soon replicated these results in cats. Then the following important evidence found that there is a high level of aluminum in the brain of AD patients with long-term dialysis, which was the first report for its linkage with AD. Since then numerous reports have prompted the suggestion that aluminum is a possible cause of AD [12]. Subsequent study using a low dose of aluminum salts to rabbits by intracerebral injection found NFTs similar to AD patients in rabbits' brain, and it is the first chronic neurotoxicity model of aluminum. Then the Aluminum Hypothesis had been the focus of intensive research efforts for decades long [12]. However the hypothesis has some unsatisfy parts: First, high aluminum levels in the brain are not found in all AD patients, and as a common characteristic in AD, the SPs are not seen in experimental Al toxicity. Second, aluminum-induced NFTs are not the same as NFTs in AD when components' details of NFTs were analyzed. Third, with increased aluminum levels, only transit dialysis dementia in renal patients is elevated, and no rising incidence of cognitive impairment and AD symptoms were seen. Yet, the Aluminum Hypothesis continues to attract the attention of a group of scientists, and aluminum continues to be viewed with concern by some of the public. More recent studies showed the neurodegenerative effects of extended exposure of experimental animals to levels of aluminum that have relevance for the human population. Moreover, aluminum-mediated neurodegeneration resulting in cognitive dysfunction has been associated with elevated amyloid precursor protein (APP) expression, amyloidβ (Aβ) deposition, hyperphosphorylation of tau, formation of intraneuronal neurofibrillary tangles (NFTs), and apoptotic neuronal death resembling those that are found with AD brain, which can highlight the relevance of Al in AD [5].

6.6.1 Aluminum and Aβ

Aβ is a 39 to 43 amino acid-long peptide derived from a larger transmembrane protein; the amyloid precursor protein (APP) has an intrinsic tendency to form insoluble aggregates. Mountains of studies have focused on the structure, aggregational properties and neurotoxicity of Aβ, and their roles in AD. Aluminum influences the aggregation and toxicity of Aβ [33]. In physiological buffers, Al, Fe, and Zn at 10 mM concentration strongly promoted Aβ aggregation (a rate enhancement of 100- to 1000-fold). Al appears to be the most efficient cation in promoting Aβ aggregation in vitro increasing Aβ neurotoxicity dramatically. And aluminum also inhibits proteolytic degradation of Aβ peptide by cathepsin D in vitro. It is widely believed that amyloid-Al complexes are more toxic than Al or amyloid on their own and consequently play a key role in the etiology of AD [37].

Systemic aluminum can induce AD-like behavioral deficits in treated rats. Chronic exposure to dietary Al not only results behavioral deficits, but leads to elevated levels of amyloid precursor protein, and these elevated levels have been correlated to α- and β-secretase subtypes, which together appeared to have led to increased levels of Aβ1-42. In addition, with increasing accumulation of aluminum in the brain, an elevated burden of amyloid plaques was observed in patients with renal failure. Yumoto et al. [36] examined the presence of Al at autopsy of five AD patients using energy-dispersive X-ray spectroscopy combined with transmission electron microscopy (TEM-EDX). The results demonstrated colocalization of Al and Aβ peptides in amyloid fibers in the cores of senile plaques. There is also evidence that Al may alter the dynamics of Aβ. The core center of amyloid plaques is known to contain an overabundance of Aβ42, which is less soluble than the more abundant Aβ40. There is now clear evidence that when Al complexes with Aβ42, it reduces solubility, increases precipitation of β-sheets, and facilitates Aβ flux across the BBB. Aluminum is also known to enhance the processing of APP. It has been shown that Al accumulated in AD brain accelerates the generation of Aβ due to the faulty proteolysis of normal APP. It has been shown that APP has a domain homologous to inhibitor of bovine pancreatic trypsin, and Al inhibited the activity of serine protease inhibitors. Thus Al is indirectly involved in activating serine proteases such as a-chymotrypsin, enhancing processing of APP and leading to accumulation of Aβ and plaque formation.

6.6.2 Aluminum and NFTs

As a marker for neurodegenerative diseases such as Alzheimer's disease (AD) and ALS, NFTs are the aggregates of phosphorylated tau protein. The phosphorylated tau protein has its ability to self-assemble into filamentous structures that are the pathological hallmark of tauopathies. Many reports show that Al promotes phosphorylation of the tau protein and causes the formation of NFTs. Al exerts

hyperphosphorylation of tau depending not only on protein phosphatase-2A (PP2A) activity inhibition but caspase activation which truncates hyperphosphorylated tau. Al then binds to the truncated hyperphosphorylated tau and aggregates it into granules. High local concentrations of Al/truncated hyperphosphorylated tau may trigger polymerization to form NFTs. Some of the NFTs are getting larger enough to kill the neurons [31]. However, there are a few differences in reports about tau aggregates and its toxicity. The reports show that tau aggregates by Al are in amorphous form, not in common fibrillary form. Al can produce toxicity to the fibroblasts that expressed tau. However, tau did not aggregate in these cells, but neurofilaments do aggregate in aluminum-treated cells [14]. Also the Al-induced increased in tau immunoreactivity was observed in human neuroblastoma cells, without an effect on cell viability [21].

Some studies reported that Al causes neurofilament monomers of tau in soluble form which results in the formation of aggregates into nonfibrillar material. Al also induces to form fibrillary bundles of neurofilaments and to form NFTs [14, 28].

6.6.3 Aluminum and Cell Death

Apoptosis is one of the mechanisms contributing to neuronal loss in AD. Neurons in the cortex and hippocampus of the AD brain show evidence of DNA damage, nuclear apoptotic bodies, and chromatin condensation. Multiple studies have shown that Al induces cell death stimulus similar to that of AD [10, 24, 25]. Al induces cytochrome c release from mitochondria, a decrease in Bcl-2 in both mitochondria and endoplasmic reticulum, Bax translocation into mitochondria, activation of caspase-3, and DNA fragmentation [11]. The released cytochrome c from mitochondria binds to Apaf-1 and initiates Al-induced apoptosis cascade [24]. The formed complex activates caspase-9, which in turn activates the effector caspase that is caspase-3. The released cytochrome c is involved in three distinct pathways like opening of the mitochondrial transition pore (MTP), translocation of mitochondria of the proapoptogenic Bax which can form the channel by itself, and interaction of Bax with the voltage-dependent anion channel (VDAC) to form a larger channel which is permeable to cytochrome c. The primary event in the apoptosis is considered as the mitochondrial changes following cytotoxic stimuli [29]. Furthermore, the studies show that the activation of SAPK/JNK (stress-activated protein kinase or c-Jun N-terminal kinase) signal transduction pathway is also caused by the induction of Al and results in apoptosis [9]. Apoptosis is believed to be the general mechanism of Al toxicity to the cells. Treatment with Al shows some characteristic features of apoptosis like shrinkage of cell bodies, hypercondensed and irregularly shaped chromatin, and extensive fragmentation of chromatin and DNA [11, 16]. Al induces apoptosis in the astrocytes further leading to the neuronal death by the loss of the neurotrophic support [27].

6.7 Epidemiological Evidence of a Relation Between Aluminum Intake in Daily Life and Alzheimer's Disease

Early reports on neurodegenerative effects of Al such as those with dialysis dementia involved relatively brief exposure to high levels of Al. More recently and more controversially, adverse effects in daily exposures to lower levels of Al have been described. Because of the difficulties in accurately assessing chronic dietary Al exposure, there have only been few epidemiological studies on the effects of aluminum in food in the general population. A pilot study including 23 case-control pairs reported potential positive results. Although the crude odds ratio for AD in subjects who consumed foods containing high levels of aluminum was 2.0 compared to those who preferred a fresh food diet, ORs were unstable and not statistically significant in this study [15]. Moreover, some important confounders such as renal function and vitamin deficiencies were not considered. Some foods containing high levels of Al like tea may contribute up to 50% of the total daily Al intake in some countries [35]. Yet, several studies found that there is no significant link between tea consumption and risk of AD. So, it is controversial to the possibility of a link between aluminum in the diet and AD.

Although drinking water is a minor contributor to the whole Al exposure in humans, numerous population studies link Al content of drinking water to risk of AD. In 1989, Martyn et al. performed a study of the incidence of AD in relation to aluminum levels in drinking water over the previous 10 years. The study found that the incidence of probable AD was 1.5 times higher in areas where the mean aluminum concentration exceeded 0.11 mg/L than in areas with concentrations of <0.01 mg/L, and there is no relationship between other types of dementia or epilepsy and aluminum levels in water [17]. It should be noted that not all AD patients had an equal probability of being included in the analysis; the population was not representative.

The association was found between aluminum in drinking water, and death rates from the neurodegenerative disease in Norway that showed relative risks for dementia in males are 1.00, 1.15, and 1.32 for low, medium, and high levels of aluminum in drinking water, respectively; the corresponding values for women were 1.00, 1.19, and 1.42. Frecker [8] confirmed geographic distributions of dementia mortality in Newfoundland related to aluminum levels in drinking water. However, the authors cautioned that these associations were ecological, serving to generate hypotheses for further study.

A case-control study conducted by Neri and Hewitt using hospital discharge data found a relative risk of 1.46 for aluminum concentrations of ≥0.200 mg/L compared to <0.01 mg/L [22]. The study was really ecological in that no additional adjustments were made for confounding factors except for age and sex. Based on the Ontario Longitudinal Study of Aging where 2000 men have been followed for about 30 years, Forbes et al. explored the relationship between Al, fluoride, and other constituents in drinking water and cognitive function. The research data showed that

the RR was 2.72 for men in areas with high Al and low fluoride concentrations in drinking water, compared to those with low Al and high fluoride levels. McLachlan et al. conducted a case-control study to investigate the relationship between AD and exposure to aluminum in drinking water. AD was diagnosed by autoptical histopathological analysis. Al concentration in drinking water at last residence before death was used as the measure of exposure [20]. Research data showed an OR was 1.7 for subjects in areas where levels of aluminum are ≥100 μg/L in drinking water. The authors later obtained even larger estimates (OR of 2.5 or greater) on the weighted residential history in the analysis [20].This is the only study based on neuropathologically confirmed cases of AD, which is a strength.

In France, Rondeau et al. [23] utilized the data from the Paquid cohort study to examine the link between aluminum and silica in drinking water and the risk of dementia and AD [23]. The analysis included 2698 subjects, aged 65 years and over. Al concentrations in drinking water ranged from 0.001 to 0.459 mg/L, and, for silica, 4.2–22.4 mg/L in drinking water. Over an 8-year follow-up, all new cases of dementia and AD were recorded. The analysis of data adjusted for age, gender, educational level, place of residence, and wine consumption revealed that the RR of dementia was 1.99 (95% CI: 1.20–3.26) for individuals who lived in areas with aluminum concentration >0.1 mg/L. For AD the adjusted RR was 2.14 (95% CI: 1.21–3.80). The concentration of silica in drinking water appeared to exert a protective effect in the development of AD (RR = 0.73, 95% CI 0.55–0.99, $P = 0.04$). Although no dose-response effect was found, the conclusions were made that Al concentration >0.1 mg/L in drinking water may be a risk factor for dementia and AD.

Several studies showed lack of significant association between AD in human populations and aluminum levels in their drinking water. Wettstein et al. [34] compared the cognitive skills between two groups in districts with high (98 μg/L) or low (4 μg/L) aluminum concentrations in their drinking water. No substantial differences were found in cognitive impairment between the high- and low-exposure groups. Urinary aluminum and serum aluminum levels showed no significant difference between ten AD patients and ten controls in both areas. However, the significance of these negative results might be limited by the fact that the highest concentration of aluminum in drinking water was below 100 μg/L [34]. Likewise, Martyn et al. [18] found no association between the risk of AD and higher Al concentrations in drinking water in a case-control study. One hundred and six men with early-onset AD were identified as cases in the study. And 99 men with other dementing illnesses, 226 men with brain cancer, and 441 men with other diseases of the nervous system were included as controls that may be deceased research sensitivity. And it should be noted that cases of early-onset AD are more affected by their genetic background than patients with sporadic AD [18]. Forster DP et al. got similar negative results whose study was also based on early-onset AD patients. Early-onset AD patients are more likely to contain mutations in their AbetaPP and/or presenilin genes, being more affected by their genetic constitution rather than by environmental influences [7].

Despite a voluminous literature, there are completely opposite assertions on the relation between AD and aluminum. Some researchers thought that chronic aluminum intake can cause Alzheimer's disease; the opposition concluded that lifetime exposure to Al is not likely to be an important risk factor for AD. The contradictory results are in part due to the great difficulty in unambiguous interpretation of epidemiological findings. Above studies are limited by methodological issues in investigation on the relationship between aluminum in drinking water supplies and the risk of developing AD. The issues include the absence of individual exposure data, poor outcome ascertainment, failure to adjust for important confounders, and small sample sizes. Thus, findings from well-defined laboratory conditions and those from population studies are not yet sufficiently and conclusively correlated so as to result in a unanimous recognition of the hazards of environmental aluminum. Moreover it is controversial whether research data concerning aluminum's role in AD satisfy Hill's criteria for causality or not [32]. These conditions illustrate the need for more study rather than more debates.

6.8 Conclusions

Based on the above data and arguments, the neurotoxic effects of Al are beyond any doubt, and Al as a factor in AD cannot be discarded. This is mainly because AD is a multifactorial disease, and to date the specific etiologies of AD are unknown. Thus, the Al hypothesis, along with other hypotheses, continues to survive. Since the accumulation of Al may occur in prodromal stages of AD, we propose that Al in daily life may initiate and promote the AD disease process; even at the very least it exacerbates the neurodegenerative process.

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