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Review

Prolonged exposure to low levels of aluminum leads to changes associated with brain aging and neurodegeneration

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ABSTRACT

Aluminum is one of the most common metal elements in the earth's crust. It is not an essential element for life and has commonly been thought of as a rather inert and insoluble mineral. Therefore, it has often been regarded as not posing a significant health hazard. In consequence, aluminum-containing agents been used in many food processing steps and also in removal by flocculation of particulate organic matter from water. In recent years, acid rain has tended to mobilize aluminum-containing minerals into a more soluble form, ionic Al^{3+}, which has found their way into many reservoirs that constitute residential drinking water resources. As a result, the human body burden of aluminum has increased. Epidemiological studies suggest that aluminum may not be as innocuous as was previously thought and that aluminum may actively promote the onset and progression of Alzheimer's disease. Epidemiological data is strengthened by experimental evidence of aluminum exposure leading to excess inflammatory activity within the brain. Such apparently irrelevant immune activity unprovoked by an exogenous infectious agent characterizes the aging brain and is even more pronounced in several neurodegenerative diseases. The causation of most of these age-related neurological disorders is not understood but since they are generally not genetic, one must assume that their development is underlain by unknown environmental factors. There is an increasing and coherent body of evidence that implicates aluminum as being one such significant factor. Evidence is outlined supporting the concept of aluminum's involvement in hastening brain aging. This acceleration would then inevitably lead to increased incidence of specific age-related neurological diseases.

Contents

1. The environmental presence of aluminum 00
2. Transient exposure to high levels of aluminum can lead to clinical neurotoxicity 00
3. Cerebral inflammation is elevated with aging, and further intensified in many chronic neurological disorders 00
4. Epidemiology suggests a relation between aluminum intake and the prevalence of Alzheimer's disease 00
5. Aluminum and neurodegenerative disorders other than Alzheimer's disease 00
6. Findings from animal models reinforce an association between aluminum and adverse neurological changes 00
7. Physiological and molecular events underlying aluminum neurotoxicity 00
8. Why do the neurotoxic consequences of low levels of aluminum remain controversial? 00
9. Conclusions 00
Conflict of interest 00
Uncited references 00
References 00

1. The environmental presence of aluminum

Aluminum (Al) is the third most abundant element found in the earth's crust (Priest et al., 1988). In 1825 that this metal was isolated in its elemental form by the Danish physicist Hans Oersted (Sigel and Sigel, 1988). Al products have many modern applications.

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Adding aluminum sulphate and lime to water causes aluminum hydroxide formation, which leads to settling of pollutants. Al containing agents are also commonly found as food and medication additives. Infant formulae are especially rich in aluminum (Dabeka et al., 2010; Burrell and Exley, 2010). Concentrations as high as 1.8 mM Al can be reached in the juice resulting when acidic fruit is boiled in aluminum cookware (Fimreite et al., 1997). 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., 2004).

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). Furthermore, the growing prevalence of acid rain resulting from fossil fuel combustion can effect to the discharge of larger amounts of Al salts from insoluble minerals, leading to greater bioavailability (Smith, 1996).

2. Transient exposure to high levels of aluminum can lead to clinical neurotoxicity

The possibility of Al being a contributing agent toward the promotion of neurological disease was initially raised by a number of clinical studies suggesting that aluminum compounds present within the body, are not harmless. Thus, aluminum-induced dialysis encephalopathy following hemodialysis is accompanied by heightened levels of Al in the brain (Russo et al., 1992). Improvement of clinical status was expedited 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). Ingestion of Al salts led to the deposition of Al compounds in the brain (Bowdler et al., 1979). Aluminum-induced encephalopathy has also been found in patients with kidney failure, treated with bladder irrigation using 1% alum (Phelps et al., 1999). A type of encephalopathy has been reported in workers in the aluminum industry, characterized by intellectual deficits, loss of muscle control, tremor and spinocerebellar degeneration (Polizzi et al., 2002). These reports are evidence that excessive levels of aluminum can have deleterious effects on human health. Anomalous 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).

In the 1940s and 1950s, 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). Despite the finding that human subjects suffering from silicosis, did not significantly benefit from this treatment (Kennedy, 1956), the procedure was described as beneficial in an animal model of silicosis (Dubois et al., 1988). Subsequently the harmful effects of inhaled Al, especially upon brain function, were reported (Rifat et al., 1990). More recently, a major accidental exposure of a rather large population to Al has taken place in Camelford, UK. This was due to the inadvertent release of large amounts of Al sulphate into the local water supply. The neurological consequences from this escape are still being studied but there is already significant evidence of harmful effects on the nervous system in some of the exposed population (Altmann et al., 1999). Histopathological examination of a person who was exposed to Al sulphate in Camelford and subsequently died of an undetermined neurological condition, revealed early-onset beta amyloid angiopathy in the cerebral cortical and leptomeningeal blood vessels. High Al concentrations were present in the more seriously disturbed regions of the cortex (Exley and Esiri, 2006).

Correlative changes are never sufficient to conclusively demonstrate causation. It has been proposed that that Al entry into the brain is a secondary epiphenomenon, consequent to damage to the blood–brain barrier. However, dialysis encephalopathy can be treated with some success using desferrioxamine chelation, and this implies that Al is directly toxic (McLachlan et al., 1991). These early results have not been followed up, perhaps in part due to the adverse side effects of desferrioxamine treatment which commonly include muscle pain, nausea, and erythema and more rarely, visual deficits. In addition, there may be a lack of interest by pharmaceutical companies in a drug that is not patentable. Treatment of aluminum-related bone disease using desferrioxamine can mobilize Al from deposits in bone, leading to elevated serum Al that led to the initiation of dialysis dementia (Sherrard et al., 1988). While desferrioxamine is not a specific Al chelator, in both of these occurrences, a causal relation between high circulating levels of Al and dementia was indicated. Other evidence of the neurotoxicity of relatively high levels of Al comes from clinical reports. One such case involving a fatal outcome, implicated aluminum-containing cements used in treatment of inner ear disorders (Reusche and Seydel, 1993). Another report concerns a chronic renal failure patient, who was treated phosphate-binding Al-hydroxy gels for a prolonged period. This patient developed Al-induced encephalopathy nine months prior to death, and post-mortem neuropathology revealed increased proliferation of microglia and astrocytes in some brain regions (Shirabe et al., 2002).

3. Cerebral inflammation is elevated with aging, and further intensified in many chronic neurological disorders

Aging of the brain is typically accompanied by increased levels of inflammation (David et al., 1997; Sharman et al., 2004). Neuroinflammatory processes become more marked during normal aging despite the lack of recognizable exogenous immune stimuli (Sharman et al., 2008; Lucin and Wyss-Coray, 2009). A further exacerbation of inflammatory events is thought to significantly contribute to pathogenic changes associated with many age-related neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). The number of activated astrocytes is elevated in AD and these changes are found in conjunction with senile plaques (Cullen, 1997). In the hippocampus of AD patients, there is an up-regulation of expression of pro-inflammatory genes (Colangelo et al., 2002), and concentrations of inflammatory cytokines are also elevated in the brain (Zhao et al., 2003) and cerebrospinal fluid (Sun et al., 2003).

AD is associated with brain depositions of the toxic amyloid β-peptide (Aβ), which is produced by proteolytic breakdown of from amyloid-β precursor protein (AβPP). Reactive microglia, producing inflammatory cytokines and acute phase proteins, are found in proximity to Aβ-containing neuritic plaques (Mrak et al., 1995; Styren et al., 1998) in the AD brain. Aluminum salts can promote Aβ aggregation in vitro (Exley, 1997; Bondy and Truong, 1998; Bolognin et al., 2011), and treatment of transgenic mice over-expressing AβPP with Al salts in the drinking water, leads to

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oxidative stress, Aβ deposition, and plaque formation in the brain (Pratico et al., 2002). More recent studies on Al and the promotion of Alzheimer pathology have led to conflicting results (Akiyama et al., 2012). An emerging generalization seems to be that aluminum's behavioral effects are clearest in normal aging animals while harder to detect in mutant strains of animals that are already genetically predisposed to plaque formation and exhibit marked memory deficits (Ribes et al., 2008).

PD is a neurological disease whose hallmarks include abnormally elevated levels of both oxidative and inflammatory events (Selley, 2005). This disorder is also characterized by microglial activation and high levels of inflammatory cytokines (Nagatsu and Sawada, 2005). Non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the possibility of developing PD (Hald et al., 2007).

When mice are treated with a systemic inflammatory stimulus such as lipopolysaccharide (LPS), levels of inflammatory cytokines are briefly elevated in serum and liver, but these return to basal levels within 1 week. However, after such treatment inflammatory cytokines are maintained at high levels in the brain for over 10 months, a significant fraction of the entire mouse lifespan. This increase is associated with both microglial activation and continuing neuronal death (Qin et al., 2007). These findings provide a clue as to why the aged brain shows evidence of continuing inflammation (Bondy and Sharman, 2010). The consequences of prolonged exposure to relatively low levels of Al are difficult to pinpoint of transient inflammatory events including infections involving the whole body, may be maintained in the CNS for an extended period (Shi et al., 2003; Bilbo et al., 2005; Galic et al., 2008). This suggests that inflammation can be a self-promoting process and this may play an important role in advancing neurodegeneration (Block et al., 2005; Lucin and Wyss-Coray, 2009). Many age-related neurological diseases appear to be associated with an even higher level of inflammation than that observed in normal brain aging (Bondy, 2010).

4. Epidemiology suggests a relation between aluminum intake and the prevalence of Alzheimer's disease

Early reports of the neurotoxicity of Al such as those with dialysis dementia involved exposure to relatively high levels of Al. More recently and more controversially, the potential health effects of more chronic exposures to low levels of Al have provoked apprehension. The finding of high levels of Al in the brains of patients with AD relative to controls has been reported [see above] and high Al levels are also found in other less common neurological disorders including the Guamanian Parkinsonian-ALS complex and Hallervorden-Spatz disease (Eidelberg et al., 1987; Garruto et al., 1988). This has raised the issue of whether the metal may play a contributory role in the initiation and progression of a variety of neurological disorders (Kawahara and Kato-Negishi, 2011).

Chelation therapy in order to reduce the Al burden in AD patients has been reported as beneficial (McLachlan et al., 1991) and new Al-specific chelators for potential use in AD treatment have recently been developed (Shin et al., 2003).

The most consistent indication of a link between exposure to Al and neurodegenerative diseases is the growing number of population studies linking the Al content of drinking water as being proportional to the degree of incidence of neurological disease. An early epidemiological study by McLachlan et al. (1996) correlated the risk of developing Alzheimer's disease with residing in areas where Al concentrations in the municipal drinking water are 100 μg/L or greater. A dose–response relationship between the concentration of Al in the drinking water and risk of developing AD was found. A more recent work, examining elderly populations exposed to Al in drinking water, also reported a similar link between exposure and the prevalence of AD (Rondeau et al., 2009).

The consequences of prolonged exposure to relatively low levels of Al are difficult to pinpoint as they often involve seeking evidence of an altered incidence of relatively common neurological diseases such as sporadic AD. However, a comprehensive literature survey assembling results from many sources and many areas, has found thirteen reports of a significant association between living in areas where Al concentrations in the municipal drinking water supplies are relatively high and an increased incidence of AD (Flaten, 2001). A more recent overview points to the possibility that conflicting results may in part be due to lack of consideration of silicate levels in drinking water in some reports, which, by complexing Al, could have a protective effect (Krewski et al., 2007).

Thus, while the mechanism underlying the means effects by which Al exerts its effects is uncertain, in many instances Al has been shown to promote events connected to neurodegenerative changes in AD. Some occupational epidemiological studies have focused on specific groups of workers such as some groups of welders exposed to high levels of Al. While some reports have found no significant correlation between Al inhalation among welders and neurobehavioral performance (Kiesswetter et al., 2009). However, another group has described significant dose-related behavioral deficits in Al welders (Giorgianni et al., 2012). This latter report emphasized that the most susceptible tests involved complex attention and memory performance.

The case for a causal relation of the association between Al exposure and AD is reinforced by findings of excessive levels of Al in post-mortem analyses of brain tissue from AD patients. The original description of this connection (Perl and Brody, 1980) was disputed due to the problem of obtaining accurate Al analyses and the probability of sample contamination (Bjertness et al., 1996). However, a range of more advanced analytical procedures including laser microprobe mass analysis (Bouras et al., 1997), instrumental neutron activation (Andrasi et al., 2005), an improved graphite furnace atomic absorption method (Xu et al., 1992) or energy-dispersive X-ray spectroscopy combined with transmission electron microscopy (Yumoto et al., 2009), have all essentially confirmed the original report. Laser microprobe mass analysis revealed the Al to be largely situated within the neurofibrillary tangles associated with AD (Bouras et al., 1997). The relation between AD and Al seems to be stronger than that for other neurological diseases but this may be because of the much higher prevalence of AD relative to most other neurodegenerative diseases, which allows more precise analysis of epidemiological data on AD than is the case with less common disorders. However, AD is also associated with other metal imbalances such as major depression of copper levels and the issue of causality remains elusive (Akatsu et al., 2012; Exley et al., 2012).

5. Aluminum and neurodegenerative disorders other than Alzheimer's disease

The connection between Al and other less prevalent neurological disorders is uncertain. There is however a series of clinical articles reporting that use of vaccines may be associated with increased incidence of multiple sclerosis. Most vaccines either contain alum or are used in conjunction with alum-containing adjuvants (Girard, 2005; Sutton et al., 2009; Chang et al., 2010; Alvarez-Soria et al., 2011; Shoenfeld and Agmon-Levin, 2011). Al excretion has been reported as elevated in MS patients (Exley et al., 2006). On the other hand, Al-containing adjuvants within a vaccine have also been suggested to have prophylactic value in the treatment of MS (Wållberg et al., 2003).

There is also evidence linking Al and Parkinson's disease, PD. An association has been made between the frequency of gastric ulcers, and PD, and it has been proposed that this linkage might be due to the higher usage of Al-containing antacids by those suffering from ulcers (Altschuler, 1999). Other indirect evidence in support

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of a connection between Al and PD is the ability of Al to activate monoamine oxidase B. This enzyme is elevated with age and further raised in PD (Zatta et al., 1999) and monoamine oxidase B is able to promote alpha-synuclein fibril formation (Burke et al., 2008). It has been proposed that this may account for the association between neurotoxic metals and PD (Uversky et al., 2001). The triggering of inflammatory processes by activation of the transcription factor NF-κB was found to occur in a synergistic manner after simultaneous treatment of experimental animals with a dopaminergic neurotoxin, MPTP and low levels of Al in drinking water (Li et al., 2008).

Neuropathological changes and motor deficits resembling those found in ALS have been have been found in aluminum-dosed animal models. Specifically, injection of Al-containing adjuvants at levels comparable to those that are administered to human adults, resulted in the death of motor neurons, impairments in motor function, decrements in spatial memory capacity in young mice and significant increases in activated astrocytes and microglia (Petrik et al., 2007; Shaw and Petrik, 2009). Blood and urine levels of Al may also be elevated in ALS (Perl et al., 1982) but there is disagreement concerning this (Qureshi et al., 2008).

6. Findings from animal models reinforce an association between aluminum and adverse neurological changes

Numerous experimental animal models where systemically administered Al caused behavioral deficits, support clinical findings on aluminum neurotoxicity. These include reports of incoordination (Bowdler et al., 1979), and changes in reactivity and neuropathological changes reminiscent of those found with brain aging (Miu et al., 2004).

Many of these studies have involved treatment with quantities of Al that are not commonly come across among human populations. However, some studies that better reflect common human exposures have been performed using relatively long treatment with levels of Al found in some water supplies or dietary exposures paralleling human intake. One such study found evidence for elevated levels of inflammatory activity within brain tissue (Campbell et al., 2004), which included heightened levels of inflammatory cytokines, nitric oxide synthetase and glial fibrillary astrocytic protein (GFAP) a marker of astrocytic activation (Yokel and O'Callaghan, 1998; Walton, 2009a). These changes were found after Al salts had been in the drinking water of mice for three months at concentrations below those found in some residential drinking water supplies. Additional persuasive data on the probable harmfulness of Al, comes from observations of cognitive and neuropathological changes characteristic of AD in aged rats after chronic exposure to Al equivalent to Al intake by some human populations (Walton, 2009b, 2012; Walton and Wang, 2009).

If the progressive inflammatory changes that characterize neurosenescence were further promoted by the extended presence of low levels of Al, this could further elevate the excess inflammatory events associated with the progression of many age-related neurodegenerative disorders. Al may act principally by promoting the rate of brain aging. This acceleration could form a platform to secondarily facilitate an increased incidence of a wide range of specific neurodegenerative diseases.

7. Physiological and molecular events underlying aluminum neurotoxicity

The development of a clear mechanistic understanding of the mechanisms underlying Al neurotoxicity remains elusive. Despite the chemical inertness of its salts, there are many potential mechanisms by which Al can promote neurotoxic events (Tomljenovic, 2011). The induction of glial activation and initiation of macrophage responsivity by Al complexes has been described several times (Evans et al., 1992; Gorell et al., 1999; Platt et al., 2001). These outcomes resemble the neuropathological findings at autopsy of a patient who had developed dialysis encephalopathy (Shirabe et al., 2002). Since aluminum salts can provoke inflammatory glial responses in isolated systems as well as in intact animals, it is likely that they can act directly upon responsive cells (Campbell et al., 2002).

Overall, there is a significant boy of literature showing that Al exposure leads to higher levels of inflammatory activity within the brain. It is especially striking that when TNF-α is raised in many tissues by a systemic inflammatory stimulus, it remains elevated in brain much longer than in other organs and does not return to resting levels for an extended period (Qin et al., 2007). In consequence, the aging brain can gradually accumulate evidence of prior insults until a permanently damaging degree of inflammatory activity is reached and maintained.

Aluminum is also capable of promoting free radical generation, despite the fact that it is not a valence-labile metal and does not have a strong affinity for sulfhydryl radicals. It may act by catalyzing the redox activity of trace amounts of iron. This ability to potentiate the pro-oxidant properties of iron can even be found in the absence of all biological tissue or protein (Bondy et al., 1998). Its mechanism of action may by involve providing a colloidal surface for the sequestration of iron leading to Fenton transformations (Bondy, 2009). Such promotion of iron's pro-oxidant potential by an apparently inert mineral has also been shown for silica fibers (Napierska et al., 2012). It has been proposed that, since aluminum has an unusually high charge density (Z^2/r), this can account for its ability to compact A-T rich chromatin domains leading to repression of specific genes (Lukiw, 2010)

8. Why do the neurotoxic consequences of low levels of aluminum remain controversial?

Interest in this subject is continuous but never breaks through to an unequivocal recognition of the hazards of environmental Al and for the need to take more regulatory action. An examination of the history of lead toxicity can give clues that may help understanding of some of the reasons behind this failure to reach a "critical take-off velocity." Lead has been used in manufacturing for over 3000 years and has been intermittently known to be neurotoxic since 700 B.C. Its prevalence has risen greatly in the last 200 years and, in the last two decades the harmfulness of even low levels of lead has been widely recognized. Now, major legislative efforts to minimize lead exposure have been effected. However, this was preceded by a period of heated controversy during which the lead industry accused leading scientists conducting low level lead research, of bias and fraud (summarized in Needleman, 2008).

In contrast, Al has only had widespread industrial use for just over a century. As in the case of lead, the neurotoxicity of high levels of Al is not disputed. However, also paralleling the situation for lead, the toxicity of low levels of Al is fiercely contested since major economic forces are concerned. Currently, no major efforts to minimize Al levels in food or drinking water are being legislatively considered. The much shorter history of Al usage means that we may be at an earlier stage of perception of its hazards to human health than is the case with lead. It is to be hoped that the next step in the evolution of the recognition of the neurotoxicity of environmental aluminum, will soon emerge.

9. Conclusions

Although the capacity of ingested aluminum to further the onset and progression of neurodegenerative disease remains unsettled, the following conclusions are pertinent and indisputable.

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(i) Al is widespread in the environment, absorbed by humans and can reach the brain.
(ii) A relatively short exposure to high levels of Al can lead to clear cut clinical signs of damage to the CNS.
(iii) Levels of intrinsic inflammatory activity increase with brain aging and this is further aggravated in many age-related neurodegenerative conditions.
(iv) Low levels of Al in the drinking water of experimental animals that parallel those found in some human exposures can elevate of inflammatory activity within the brain.

The median age in the United States is lengthening leading to the prospect of a growing incidence of extended neurodegenerative ailments including AD, PD ALS and MS. These are in the main, non-genetic, idiopathic disorders. This indicates that they are often initiated by unknown environmental factors. The causative agent of none of these diseases has been identified. Long latent periods may take place between exposure to a harmful environmental agent and the materialization of clinical symptoms. This can complicate the identification of the original factors initiating the disease process. Since aging forms an indispensable basis for the development of neurodegenerative disorders, an acceleration of changes taking place during normal brain aging, could speed up the time of the onset and thus the incidence of all such disorders. A possible sequence of events by which Al could further age-related neurological changes are suggested in Fig. 1.

One of the most promising approaches to alleviation of the societal consequences of progressive neurodegenerative diseases lies in the recognition and remediation of those environmental factors, which hasten changes accompanying normal brain aging.

The simplest way of accounting for much of the data concerning Al neurotoxicity is the concept that Al can accelerate the evolution of the aging process. This acceleration could give a reason for the epidemiological relation between Al and Alzheimer's disease, which affects a large proportion of the very elderly. It could also account for the more tenuous connection that has been proposed between Al and a range of less common age-dependent neurological diseases. The premise behind this overview is that Al drives a non-selective component of senescence, namely an elevated state of immune reactivity leading to extended neuroinflammation. This state of futile inflammatory activity could form a foundation for the enhancement and progression of more distinct neurological conditions.

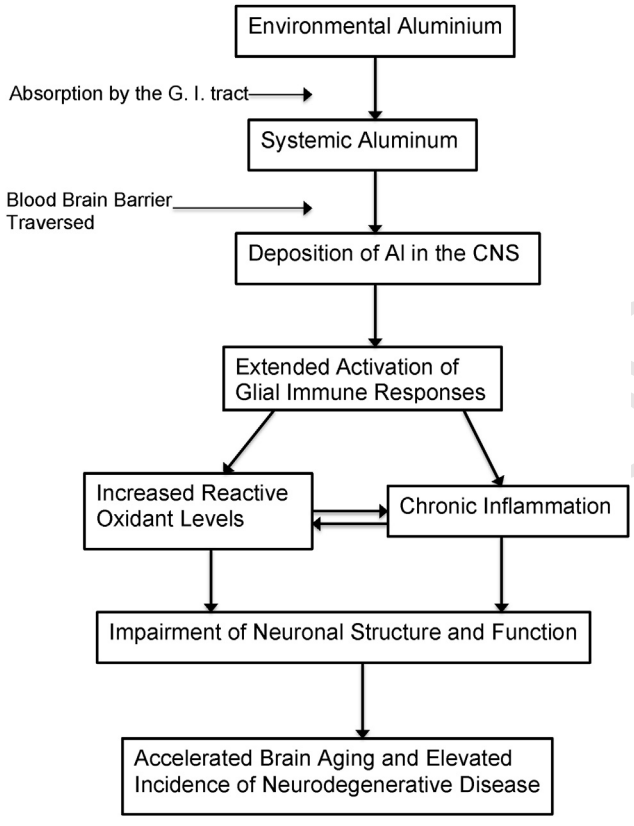

Fig. 1. Postulated sequence of events by which Al could enhance progression of age-related neurological changes.

Conflict of interest

The author has no conflict of interest of either and intellectual or commercial nature, in the research described in this manuscript.

Uncited references

Block et al. (2007), Bondy and Truong (1999), Dabeka et al. (2011), Gorell et al. (1988), Versieck and Cornelis (1980), Versieck and Cornelis (1989) and Yokel et al. (2001).

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