Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 6 (55) No. 2 - 2013

ALUMINIUM – A CHEMICAL NEUROTOXIC AGENT

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Abstract: *This work is a synthesis of expert studies that describe-induced toxicity aluminum in humans and animals, using different routes of administration. Due to its toxicity, aluminium, is the impugned in the pathogenesis of certain diseases, including Alzheimer's disease, encephalopathy, patients with dialysis encephalopathy, aplastic bone disease osteomalacia, microcytic anemia, myopathy, pulmonary fibrosis. Alzheimer's is currently one of the most serious diseases neurodegenerative diseases and the leading cause of dementia. It affects nearly 15.1 million people worldwide [2].*

Key words: *aluminum, Alzheimer's disease, encephalopathy.*

1. Introduction

Naturally, there are aluminum in ground, air, water, but add-in in the form of water purification agent in processed food, cosmetics, (toothpaste, antiperspirants), as adjuvants in the formulas given to infants as well as in the pharmaceutical industry.

In 1912, Food Drug Administration u.s. &, spared more substances from food safety tests, including aluminium, which was deemed GRAS (Generally Regarded as Safe), so it has never been tested for safety and there is no restriction on the quantity and the uses of aluminium [3].

The amount of aluminum ingested daily by man is about 5 milligrams, but it can be doubled depending on the diet. Of this amount, only a small portion is absorbed, less than 10 micrograms/day.

There are occupational limits for many countries the exposure of aluminium and aluminium oxide. For non-occupational environments, levels have been set for the ingestion of food and drinking water [4].

2. Aluminum-induced toxic effects

The first describe of the toxic effects of aluminum on the SNC has been reported as early as 1921.

The brain is an organ susceptible to accumulation of metabolic errors.

Alzheimer's disease is characterized by neuronal changes regional specificity. Hauw J.J., and McDermott JR. demonstrated the presence of aluminum at

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the level of neural incriminated outbreaks in the onset of Alzheimer's disease [5, 6].

Despite this evidence, the role of aluminum in the pathogenesis of Alzheimer's disease is controversial.

Experimental researches are, however, clear evidence for the criminalization of aluminium in Alzheimer disease pathogenesis:

- lower amounts are needed to produce aluminium neurotoxicity,- the criterion may be satisfied with the amount consumed through diet;
- Al uses an active transport mechanism to traverse the brain barriers;
- ingestion of small amounts of aluminum during life favors the selective accumulation in brain tissue;
- experiments on lab animals showed that chronic intoxication with aluminum reproduce characteristic neuro-pathological signs characteristic of Alzheimer's disease [7].

3. Toxicological studies on animals

Toxicological studies on animals of aluminum compounds reported an oral 50-lethal dose (LD_{50}) between 162 and 980 mg/kgcp [8]

Berlyne GM shows that after administration of high doses of aluminum hydroxide have been reported increased levels of aluminum in the plasma and excessive deposits of aluminum in the brain, liver, heart and muscle [9].

Thorne BM, et al., demonstrates that after oral administration to rats Long Evans, elevated doses of aluminum hydroxide (1500, 2500, 3600 mg/kgcp) for 30 days, there were no signs or clinical symptoms of intoxication, note that no changes were detected in the weight or quantity of food ingested.

But Thorne et al., have observed that animals treated with elevated doses of aluminum hydroxide occurred changes in behavior: memory impairment and change ability of learning in the case of two different trials, associated with the detection of elevated aluminum concentrations at the cerebral level [10].

Dlugaszek et al., conducted a study, following long-term exposure by ingestion of aluminum in drinking water, in the form of aluminum chloride, dihidroxi-aluminium, sodium carbonate or aluminum hydroxide.

Were dosed orally ingested aluminum distribution and changes in the tissues?

The total dose administered to each compound was 700 mg aluminum, over a period of time of 159 days.

The group that received aluminum hydroxide has revealed an increase in the concentration of Mg in bones, a decrease in the concentration of Fe in the stomach and a decrease of Cu in the liver and kidneys [11].

Bilkei-Gorzo, investigated the effects of aluminium on the neurotoxic Long Evans rats after oral administration, daily for 90 days of insoluble aluminum hydroxide (300 mg/kgcp), aluminium chloride solution (30 or 100 mg/kgcp) and aluminium hydroxide chelate (100 mg Al $(OH)_3$/kg + 30 mg citric acid/kg).

The ability to learn, determined by the number of rounds needed to retain maze path, has been affected in all cases, but more severely in the groups that received aluminum chloride and aluminum hydroxide.

The concentration of aluminum in the brain was increased at all groups, in particular the lot that received aluminum chloride solution.

Enzymatic determinations have revealed in the case of all tests, modifications of the acetilcolinesterazei activity.

The conclusion of the experiment was that the aqueous solutions with aluminium compounds exhibit a higher neurotoxicity, but it has been demonstrated and the

possibility that some compounds insoluble aluminium hydroxide can be absorbed by producing defeats of nervous system functions [12].

Injection of 0.3 ml of a 1% suspension of aluminum powder in liquid water tank level arahnoidian magna, from adult rabbits induced a weak progressive encephalopathy, characterized by altered posture, myoclonus and muscle weakness [13].

Were observed from 1 day to 81 days after injection, the presence of neurons with neurofibrillary degeneration (NFD) and swelling of proximal axons.

In some animals included in the experiment, the large axons was a very thin myelin sheaths or even absence, also found pathological changes in the peripheral nerves and muscles.

Neuropathological investigations have confirmed that the vulnerability of brain aluminum is a time-dependent event.

During the experiment 1-81 days neurofibrillary degeneration (NFD), appeared in the nuclei of neurons in the central nervous system, except neurons in the amygdala or striated substance.

The same study showed that large anterior horn neurons showed neurofibrillary degeneration more severely. and cause of death of animals at 2-3 months after injection was neurogenic muscular atrophy [13]. The results of this study are consistent with other studies of Klatzo I crapper DR and Wisniewski HM, which showed that the aluminum salts, induced encephalopathy with neurofibrillary degeneration, after experimental subarachnoid injection, the animals studied [14, 15, 16].

Platt et al. Immunohistochemistry studies were performed on adult rat brain after repeated intracerebroventricular injection of aluminum (5.4 or 0.68 mg / day for 5 days).

In animals followed for a period of 7 days to 6 weeks, Platt et al. have shown that aluminum is concentrated in the white matter of the neostriatum, the corner of central and cingulate gyrus.

Aluminum treated animals were detected inflammation and lesions in the central gyrus, which led to severe anterograde degeneration of cholinergic terminals in the cortex and hippocampus.

These findings suggest that increased inflammation and interference with cholinergic signaling may be ways of action by which aluminum induces memory deficits [17].

4. Toxicological studies in humans

Spofforth did the first description of the toxicity of aluminium in humans in 1921. He described such symptoms as the loss of memory, tremor, seizures and coordination problems in a 46-year-old man who worked in the metallurgic industry and who used an aluminium tool in the technological process in order to immerse hot metal with nitric acid solution [1].

Reusche et al. reported a case of encephalopathy that became fatal after the extirpation of an acoustic neurinoma where, for purposes of bone reconstruction they used cement that contained aluminium. Six weeks after the chirurgical extirpation, the 52-year-old patient presented disorders of consciousness, sub-acute coma and grand mal seizures, symptoms that were similar to those of encephalopathy occurring in dialysis patients between the 1960s and 1970s. The patient died 6 months after the symptoms occurred because of septic complications. After the autopsy, during the histopathological examination of the different sections in the Central Nervous System (CNS), they found argentophillic inclusions that contained aluminium at level of the choroid plexus epithelium, of

the neurons and of the glial cells. The lesions were found to be pathognomonic of encephalopathy in dialysed patients.

After an association was made, in 1921, between the aluminium intoxication and the occurrence of dementia, many studies tried to prove the direct relation between aluminium intoxication and the CNS lesions.

In 1962, McLaughlin et al. reported the toxic effects that aluminium had on a worker in the metallurgic industry, who had been working in a factory that processed aluminium for 13 and a half years. The man presented encephalopathy associated with epileptic seizures. The symptoms had occurred 3 years before his death: short-term memory loss and speech impairment, his death being caused by terminal bronchopneumopathy.

During the autopsy, the aluminium amounts in the brain and lungs were dosed and values of 122 were found, i.e. 20 times higher values than the normal ones [18].

In 1970, it was discovered that aluminium may cause serious health problems – the so-called post-dialysis dementia was diagnosed – induced by the high levels of aluminium in the medical equipment used. Aluminium binds with transferrin and, later on, penetrates the brain [19].

The normal plasma aluminium concentration ranges between 1 and 2 µg/L. Aluminium concentration in the lungs is higher as compared to that in the bone system and soft tissue, due to the intake of particles from the surrounding environment. Approximately 60%, 25%, 10%, 3%, 1% of the aluminium load is in the bones, lungs, muscles, liver and respectively brain. High concentrations can be tracked in case of uraemia and the highest concentrations occur in the encephalopathy of dialysed patients.

The serum aluminium concentrations that exceed 30µg/l in dialysed patients have been associated with osteomalacia and kindred diseases, whereas concentrations that exceed 80µg/l are generally associated with post-dialysis encephalopathy.

Maximum 5 mg/kg basis of desferrioxamine are administered once or twice a week for long-term treatment in chronic aluminium intoxications [20].

Toxicological studies in a case of accidental Al contamination of the drinking water in Camelford (Cornwall UK) in 1988 revealed the direct connection between aluminium consumption and the central nervous system lesions. Following contamination, more than 20,000 people were exposed to elevated concentrations of Al. The exposed residents presented different symptoms that occurred in the ten-year course of the toxicological study: brain damage and short-term loss of memory and concentration [21]. Other authors too have described high incidences of occurrence of the Alzheimer's disease in regions where the drinking water had elevated Al concentrations: Norway, Canada [22], France, England and Wales [23].

5. Aluminium-induced oxidative stress

Metals can produce free radicals in the body. Metals such as copper, iron, cadmium, arsenic, mercury, chrome, antimony, beryllium, thallium, silver, nickel and aluminium induce a toxic effect due to their ability to transfer electrons.

Table 1

The effects of Aluminium upon the CNS, modified and adapted from Link Between Aluminium and the Pathogenesis of Alzheimer's Disease: The Integration of the Aluminium and Amyloid Cascade Hypotheses by Kawahara M. and Kato-Negishi M, page 3

Affects the nucleus and gene expression
✓ DNA binding ✓ Histone-DNA binding and the induction of chromatin conformational changes ✓ Induction of DNA typological changes
Expression of the altered genes
✓ Induces the decrease in the expression of the neurofilament and tubulin ✓ Induces the decrease in the expression of the transferrin receptor ✓ Induces the alteration in the expression of the ARN-polymerase ✓ Induces the lowering in the number of mitochondrial cytochrome c oxidase receptors ✓ Induces the alteration of the calbindin-D28k expression ✓ Induces the decrease expression of the neuron growth factor (NGF) and of the Brain-Derived Neurotrophic Factor (BDNF) ✓ Induces the expression of pro-inflammatory genes and pro-apoptotic genes ✓ Induces an increase in the elevated expression of the amyloid precursor protein **(**APP) ✓ Induces the alteration of the expression of the genes of the oxidative stress markers (SOD1, glutathione reductase etc.) ✓ Induces the decrease of the expression of neprilysin ✓ Induces the alteration of the expression of β-APP-secretase (BACE1 şi BACE 2)

These free radicals resulted from metals can affect cell integrity, producing the peroxidation of the lipids in the intracellular membranes, and the cross-linking with the macromolecules in the membranes.

The free radicals of heavy metals have the tendency to form covalent links with the sulfhydryl groups, thus modifying the functions of many enzymes. Toxic metals are known to affect the permeability of cellular membranes, of sub-cellular organelles, the structure and functions of proteins and the structure of nucleic acids.

Oxydable substances in the body are represented by proteins, lipids, carbohydrates and DNA. They represent the targets of free radicals and the source of all the damages produced to the body by oxidation.

Oguz Eo, Smith MA and Katyal Ranjan et al. have conducted some experimental studies that have demonstrated the role of Al in the generation of ROS [24, 25, 26].

Love S. has demonstrated that oxidative stress is the main cause incriminated in the pathogenesis of inflammatory, metabolic, and partially in ischemic processes, but also in the degenerative diseases of the cranial nerves [27].

Brain tissues are very susceptible to oxidative stress owing to the high rate of oxygen consumption (20%), to the abundance of the polyunsaturated fatty acids in the cell membranes, to the high content of iron (Fe) and the decreased activity of the anti-oxidative enzymes in this organ.

The lesions found in the brains of Alzheimer (AD) patients are usually associated with high values of the oxidative stress, and Al has been proved to have a catalytic activity in order to produce free radicals. Moreover, the beta-amyloid

protein in the brains of Alzheimer patients amplifies the production of free radicals.

It has been demonstrated that oxidative stress induced by Al modifies lipid peroxidation and the activity of antioxidant enzymes. Julka and Gill have identified the increase of lipid peroxidation in the brain tissues of adult Wistar rats after administering 10mg/day Al (aluminium lactate) for 4 weeks [28].

Oral administering of Al acetate (4000 mg Al/kg basis and 6000 mg Al/kg basis) for 8 weeks led to the increase in the end-products of lipid peroxidation (thiobarbituric acid, or TBARS) in the brain tissue of rats. In his study, Katyal showed that aluminium treatment of the rats increased cerebral protein peroxidation [29]. In the animals used in the study, the hippocampus, the diencephalon and the cerebellum saw significant increases of the levels of end-products of the lipid peroxidation (TBARS). Oral administering of aluminium – Al (0,1 mmol / kg / day) or intra-peritoneal injecting of Al (7 mg / kg / day) for 11 weeks induced high accumulations of end-products of the lipid peroxidation in the hippocampus. Nehru and Bhalla reported high values of Al in the diencephalon in the Sprague female rats [30].

Bhalla P. proved that the accumulation of Al in the cerebellum increased the amount of end-products of the lipid peroxidation in the cerebellum of the adult rats. Oral administering of Al (100 mg / kg basis per day) for 2 months increased lipid peroxidation in the cerebellum of adult rats. Also, the level of TBARS (thiobarbituric acid) in the cerebellum increased in the rats that received intra-peritoneal injection of aluminium (7 mg Al/kg/day) for 11 weeks [30].

Nehru and collaborators identified significant increases of lipid peroxidation in the brains and cerebella of baby rats as a consequence of the exposure of pregnant female rats to aluminium chloride administered *per os* (100 mg / kg /day) for 6 weeks. The study revealed that Al induced the production of ROS (reactive oxygen species) and of the free radicals that were involved in the onset of oxidative stress in the brains of the new-born rats. The results of the study confirmed that high concentrations of Al induced oxidative stress and caused lipid peroxidation in the hippocampus, the diencephalon, the cerebellum and the brainstem. The results of the study indicated the fact that the enzyme activity of SOD (superoxide dismutase) decreased at the same time as the increase of lipid peroxidation in the hippocampus and the cerebellum. This fact was consistent with other studies that had revealed that the activity of SOD decreased significantly in the region of the hippocampus, the cerebellum and the brainstem of the animals treated with aluminium [30].

6. Antioxidant therapy in Alzheimer's disease

Antioxidants are pre-requisite of a good health condition. Nevertheless, nobody knows what the optimal amount of antioxidant supplement needed to preserve such a condition is.

The Ginkgo biloba leaf extract used to treat peripheral vascular diseases and cerebral vascular insufficiency in elderly persons has an antioxidant action and it works upon different reactive oxygen species and nitric oxide [31].

Pentoxiphyllin, piracetam and vinpocetine have a clear antioxidant capacity.

Le Bars et al., have proved that the administering of antioxidants in the diet has been associated with a decreased risk of Alzheimer's disease.

Perrig W.J. et al. associate the high plasma concentration of antioxidant

vitamins used on a study group with a better performance of the memory in elderly patients. Le Bars, P.L. et al. showed in their clinical studies of Alzheimer's disease that antioxidants have positive effects upon the progression of the disease: vitamin E in a two-year trial and Gingko biloba in a 52-week trial in the early phase of the disease [31, 32].

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