

Review

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The meaning of aluminium exposure on human health and aluminium-related diseases

Abstract: The aim of this review is to attempt to answer extremely important questions related to aluminium-related diseases. Starting from an overview on the main sources of aluminium exposure in everyday life, the principal aspects of aluminium metabolism in humans have been taken into consideration in an attempt to enlighten the main metabolic pathways utilised by trivalent metal ions in different organs. The second part of this review is focused on the available evidence concerning the pathogenetic consequences of aluminium overload in human health, with particular attention to its putative role in bone and neurodegenerative human diseases.

Keywords: aluminium; aluminium overload; aluminium-related disease; bone pathology; brain pathology.

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Introduction

In recent years, humans have probably experienced a burgeoning exposure to biologically reactive aluminium, with possible relevant consequences for human health and disease (1–3). This potentially dangerous exposure is related to a great extent to atmospheric acidification due to acid rain, which is causing a progressive acidification of the soil, followed by a massive export of aluminium from the crust of the earth to surface waters, putting vegetables, animals and humans in contact with absorbable cationic aluminium species, probably for the first time in their history (4). Owing to acid rain, numerous metal

ions, including aluminium are escaping from mineral deposits where they had been stored for billions of years as hydroxy-aluminosilicates (HAS) (5, 6), increasing the biological availability of aluminium to living organisms. According to this hypothesis, acid rain is acting as a key to the lock for aluminium release, causing its appearance in polluted waters. In Figure 1, the mobilisation of aluminium by acid rain has been schematically presented.

Another factor responsible for the recent overexposure of biota, and in particular of humans, to aluminium is represented by human activity, including the modern technology used to extract aluminium metal from its biologically-inert ores, such as cryolite (aluminium fluoride) and bauxite (native aluminium hydroxide). In fact, aluminium is characterised by a probably unrivalled versatile chemistry, testimony to which is a huge number of applications for modern living (7, 8). Aluminium compounds contact human beings as a component of many cosmetic preparations, as aluminium salts, from use in the alimentary industry and also in pharmaceutical drugs. Aluminium products, despite the metal being recognised in the 1970s as the cause of different diseases, continue to be in large use in numerous human activities and applications (2). Why is such a biologically reactive metal ion, ubiquitous in our environment, the most abundant metal in nature, not an essential element in biology? Why has biochemical evolution proceeded in the absence of biologically reactive forms of aluminium, with no essential role for aluminium in any biochemical system in any organism (7)? And what are the consequences on human health and disease of the massive exposure that humans are now experiencing to aluminium?

The aim of this review is to try to give answers to these questions, covering the main sources of aluminium exposure in our daily lives and the principal aspects of aluminium metabolism in man and trying to clarify the main metabolic pathways utilised by this trivalent metal ion in different organs. The second part of this review will focus on the available evidences regarding the possible pathogenetic consequences of aluminium overload in human

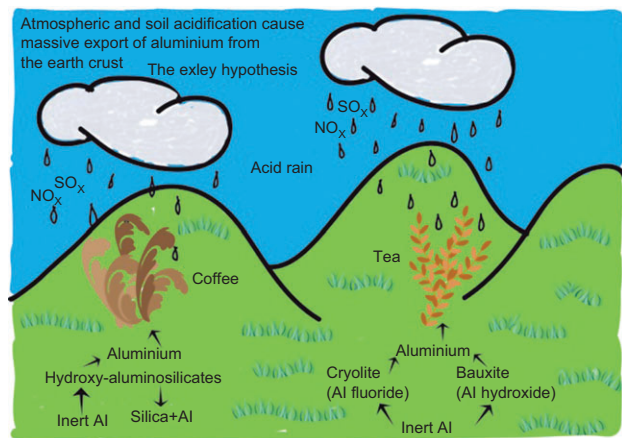


Figure 1 Mobilisation of aluminium as a consequence of acid rain.

pathology, with particular emphasis on its putative role in bone and neurodegenerative diseases.

Aluminium exposure

Aluminium in food

Aluminium is ubiquitous in the hearth environment. As a consequence, food is the primary source for aluminium intake under physiological conditions (9). The widespread presence of aluminium, both in the environment and in foodstuffs, makes it virtually impossible to avoid exposure to this metal ion (10). In fact, aluminium is a component of many items used daily, including personal hygiene products and medications.

The concentration of aluminium in food is extremely variable, due both to the original content and to food interaction with the material it contacts in storage or in cooking. For example, the aluminium content of a variety of beverages contained in aluminium cans is five to seven times higher compared to the same type of beverage from bottles (11). Most plant food has a low aluminium content, normally $<25 \mu\text{g/g}$ of dry weight. At the extremes of the spectrum, we find tomatoes, showing very low aluminium levels, from 0.2 to $1.1 \mu\text{g/g}$, and marjoram and thyme, which show very high aluminium concentrations, ranging from 500 to $1000 \mu\text{g/g}$. Soy-based milk formulas provide a potentially high aluminium source to infants (12). Plants such as tea accumulate aluminium in older leaves, which may contain as much as 3% w/w of aluminium (13), which explains the high aluminium concentrations in tea infusions (14). A high aluminium content has also been found in coffee beans, at levels comparable to those of tea leaves (15). Recently, different methods of beverage

preparation have been shown to change significantly the aluminium content in coffee infusions: the difference between a coffee beverage prepared in aluminium and one prepared in stainless steel moka pots is significant due to aluminium leaching during preparation (16).

The concentration of aluminium in animal-derived food is low, normally below $1 \mu\text{g/g}$, with higher values (about $19 \mu\text{g/g}$) reported in Swiss cheese. The results of a recent study on aluminium concentrations in milk, milk powder and cheese indicate that aluminium levels are beyond the permissible limits and suggest health hazard (17). According to the authors, the concentration depends on whether milk is kept in aluminium containers and dairy products are packed in aluminium foil. These findings suggest that all milk cans should be constructed of stainless steel and that processed cheese should be packed in glass containers, avoiding the use of aluminium foils.

Regarding the aluminium content in seafood, the increase in the aluminium content in rivers and the sea has induced numerous researchers to study the accumulation and toxicity of the metal in freshwater organisms. Crayfish have been recently shown to accumulate and store aluminium from contaminated water, the highest concentration of the metal being found in their hepatopancreas (18).

Drugs represent another relevant source of aluminium intake, the greatest potential sources being aluminium-containing antacids and buffered aspirins (19) (Table 1).

Table 1 Some sources of aluminium exposure in humans.

Source	Amount
Natural sources	2–5 mg/day
Tea leaves	0.1%–1%
Coffee from aluminium moka	0.8–1.2 mg/cup
Drinking water	0.07 mg/l
Beverages in aluminium cans	0.04–1.0 mg/l
Cooked spinach	25 mg/kg
Unprocessed food	0.1–7 mg/kg
Food additives	10–20 mg/day
Food cooked in aluminium pots	0.2–125 mg/kg
Soy-based infant milk formulas	6–11 mg/kg
Antacids	35–200 mg/dose
Buffered aspirin	9–50 mg/dose
Antidiarrhoeal drugs	36–1450 mg/dose
Antiperspirants	50–75 mg (daily exposure)
Vaccines	0.15–0.85 mg/dose
Parenteral nutrition solutions for adults	40–135 $\mu\text{g/l}$
Parenteral nutrition solutions for infants	10–270 $\mu\text{g/l}$

Bioavailability for gastrointestinal absorption should also be taken into consideration when discussing human exposure to aluminium in food and/or drugs. For example, the addition of milk to tea infusions should transform free aluminium in insoluble phosphate, thus blocking its absorption. In contrast, the addition of lemon juice to tea infusions, favouring the formation of Al^{III} -citrate complexes, will increase aluminium absorption through the intestinal barrier into the blood (20). Taken together, these data suggest that, when determining the risk assessment of aluminium in food, not only the amount of the ingested metal should be taken into account, but also the entire composition of the food, which can lead to marked differences in aluminium absorption (21).

As high aluminium levels occur in only a few foods, it is generally considered that natural sources contribute only about 2–5 mg/day and probably even less for non-tea-drinkers. Food additives play a relevant role in aluminium exposure, adding 5–100 mg/day, the highest amounts being found in aluminium baking powder products and aluminium-containing emulsifiers used for cheese (22). The contamination of food during processing, cooking and storage may result in high aluminium intake by consumers. This is particularly true when acidic foods, such as tomatoes and to different extents all vegetables, are cooked in aluminium pots, in which leaching of relevant amounts of the metal takes place, with aluminium concentrations as high as 50 mg/l (23).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has recently given a scientific opinion on the safety of aluminium from dietary intake (JECFA 74th Meeting, Rome June 14–23, 2011). In the JECFA report, the tolerable weekly intake (PTWI) for aluminium was determined and corresponded to 2 mg aluminium per kg of body weight per week. The JECFA affirms in their report that ‘The Committee noted that estimates of the contribution to overall mean dietary exposure from all sources (including natural sources, water consumption, food contact materials and food additives) were in the range of 10–140 mg/week in adult populations (0.2–2.3 mg/kg bw per week as aluminium, assuming a body weight of 60 kg)’ omissis ‘the estimated dietary exposures are related to average adult populations and high dietary exposures are generally assumed to be 2 times higher than the reported average. It also noted that children generally have higher food intake than adults when expressed on a body weight basis and therefore represent the highest potential exposure to aluminium per kilogram of body weight’ (24). These results demonstrate that in many countries, a considerable number of people, especially children, are under high aluminium exposure and are

at risk of aluminium intoxication, with possible relevant consequences on their health (25). Another source of daily aluminium intake in humans is represented by toothpastes, which have been claimed to play a role even more important than that of drinking water in determining aluminium overload in humans (26). Aluminium is generally found in municipal water as various aluminium salts are largely used as coagulants in water treatment. This treatment consists of the addition of an aluminium salt at defined pH conditions, and consequent hydroxide flocculation, sedimentation and filtration. The slow precipitation of the gelatinous $\text{Al}(\text{OH})_3$, englobing any solid particles present, such as dust and bacteria, purifies and clarifies water. This purified water is a saturated solution of aluminium hydroxide. The total aluminium and its species present in water are determined by pH and by the amount of inorganic ligands in solution (F^- , Cl^- , SO_4^{2-} and SO_4^{2-}) (27).

Aluminium in pharmaceutical products

Aluminium hydroxide, contained in numerous antacids, is generally considered to be the most common cause of iatrogenic aluminium toxicity in the Western countries. A normal therapeutic regimen of antacids contains 5 g of aluminium hydroxide per day, a dosage several hundred times higher than the amount normally ingested from food (Table 1). In particular, when associated with oral citrate, the administration of aluminium hydroxide has been reported to cause acute aluminium intoxication, clinically characterised by the development of rapid progressive encephalopathy. This condition presents with marked confusion, myoclonic seizures, coma and, in rare cases, death (28). Aluminium storage and toxicity has been reported in children affected by renal insufficiency and receiving aluminium hydroxide as a phosphate binder, who later developed encephalopathy with myoclonic seizure (29). Various studies have demonstrated that children affected by chronic renal failure under aluminium hydroxide therapy develop aluminium storage, revealed by serum albumin $>100 \mu\text{g/l}$ and increased bone aluminium concentration (29–32). Preterm infants submitted to prolonged intravenous feeding have been found at risk of aluminium intoxication, developing neurotoxicity clinically manifested in childhood with a mental development index <85 and subsequent educational problems (33). The contamination of parenteral solutions with aluminium has been reported as one of the main factors responsible for the development of metabolic bone disease in parenteral nutrition patients, particularly in preterm newborns,

and leading to osteopenic bone disease (34). Elevated concentrations of aluminium have been reported in infants receiving intravenous therapy (35) and in children undergoing protracted regimens of parenteral nutrition, caused by parenteral drug products containing aluminium as an ingredient (36). Aluminium intoxication in newborns fed by infant formulas, as a consequence of the presence of aluminium as a contaminant, has been described (37, 38). Actually, the aluminium content in premature infant formulas ranges from 100 to 900 µg/l in contrast with the aluminium content in human milk, which ranges from 4 to 65 µg/l (32).

Aluminium as a vaccine adjuvant

Some concerns have been raised in recent years regarding the possible adverse effects of aluminium in childhood vaccines on the maturation of the immune system. In fact, aluminium is used as an adjuvant in multiple childhood vaccines, including DtaP, Pediatrix (DtaP, hepatitis B, polio combination), Pentacel (DtaP, HIB, polio combination), hepatitis A, hepatitis B, *Haemophilus influenzae* B (HIB), human papilloma virus (HPV) and pneumococcal vaccines (39, 40). Recently, adjuvant aluminium hydroxide has been also associated with Gulf War syndrome, which has been hypothesized to be linked to the multiple vaccines that soldiers underwent during their participation in the Persian Gulf War (see Section 3.3).

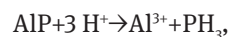
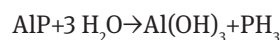
Aluminium toxicity: general mechanisms

A causal role for aluminium in human pathology has been clearly established in at least three diseases: dialysis dementia (41), osteomalacia (42) and microcytic anaemia without iron deficiency (43, 44). The principal symptoms of aluminium toxicity are:

- diminished intellectual function, forgetfulness, inability to concentrate;
- speech and language impairment;
- personality changes, altered mood, depression;
- dementia;
- visual and/or auditory hallucinations;
- osteomalacia with fracturing;
- motor disturbances;
- weakness, fatigue, mainly related to microcytic anaemia;
- epileptic seizures.

A first analysis of the clinical pictures related to chronic or acute aluminium intoxication in humans indicates that metal toxicity is mainly related to its effects on the neurological system, on bone cells and on the haematological system (Figure 2). But, even if the main targets of aluminium toxicity have been clearly identified, the intimate mechanisms undergoing aluminium toxicity need to be elucidated.

A recent review on aluminium toxicity in plants, animals and humans revealed a similar mode of aluminium action in all living organisms: the enhanced production of reactive oxygen species resulting in oxidative stress and cell death (45). Aluminium phosphide (AIP) is a potent pesticide, utilised for the protection of stored products and crops, but it has also been shown to be severely toxic to humans (46). Subjects who underwent acute exposure to aluminium phosphide presented nausea, vomiting, acute respiratory distress syndrome and altered sensorium. In some cases, the clinical picture worsened, ending with coma (47). The molecular bases of AIP toxicity have been at least in part clarified. Remembering that aluminium phosphide reacts with water or acids to release phosphine,



cell damage induced by phosphine has been demonstrated to be due to multiple interactions with the enzymatic cascade system, called the respiratory chain, situated in the membrane of the mitochondria. The first target of phosphine might be represented by the inhibition of cytochrome oxidase (48). Being cytochrome oxidase, the terminal enzyme of the mitochondrial

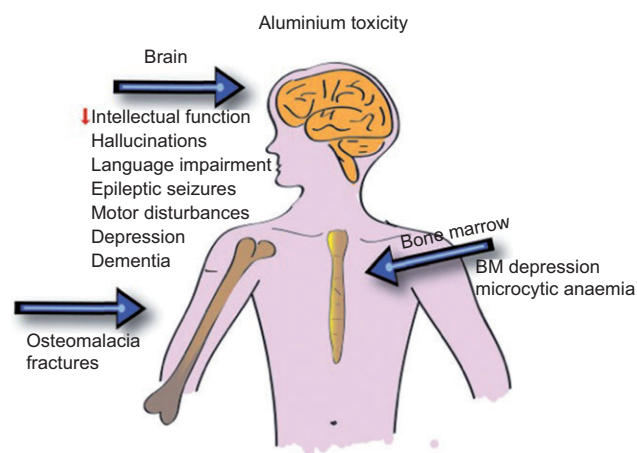


Figure 2 Principal targets of aluminium toxicity in humans.

electron transport chain, its inhibition decreases oxygen utilisation and thus aerobic metabolism, leading to ATP depletion, increased intracellular calcium levels and, eventually, cell death (49, 50). Moreover, phosphine could attack the sulphhydryl groups at the active sites of NADH dehydrogenase and succinic dehydrogenase, leading to the complete inactivation of the vital mitochondrial proteins (51). The lowered activity of succinic dehydrogenase and of NADH dehydrogenase could account for lowered mitochondrial respiration and for decreased ATP production (52).

Moreover, a mechanism depending on aluminium poisoning may lead to cell death through enhanced oxidative stress and consequent increased lipid peroxidation. The mechanism proposed to underlie this effect involves the formation of the aluminium superoxide radical ion ($\text{AlO}_2^{\cdot-}$), which could act as a pro-oxidant in catalysing the formation of hydrogen peroxide H_2O_2 , and reducing Fe^{III} to Fe^{II} (53).

Aluminium can interact with transition metals; in particular, the interaction with iron and copper enhances the production of reactive oxygen species by these two redox-active metal ions, leading to the exacerbation of cell oxidative stress and neuronal cell death (54). Recently, the interaction between aluminium and iron, regarding the evidence on toxicity and the pathological consequences in humans, has been proposed as one of the main molecular mechanisms underlying aluminium toxicity in humans (55). The potential toxic effects of aluminium as an enhancer of reactive oxygen species production, catalysed by transition metal ions, has been recently confirmed in a study on emerging strategies for the prevention of Alzheimer's disease progression (56). The intimate mechanism underlying this activity of aluminium on transition ions has not, to the best of our knowledge, been clarified yet.

Whereas the vast majority of reports regarding aluminium toxicity are related to chronic events, acute aluminium intoxication is uncommon in clinical practice. Nevertheless, acute aluminium intoxication is a well-known event because of the incidence of fatal cases. Alum bladder irrigation is one of the most frequently reported causes of encephalopathy due to acute aluminium toxicity (57).

Bone pathology

The metabolic effects of the uptake of aluminium-transferrin complexes (Al-Tf) differ from those observed after uptake of aluminium-citrate (Al-ci) complexes, which suggests that Al-Tf might sequester aluminium in intracellular

compartments different from Al-ci. Therefore, different mechanisms and different molecular pathways probably underlay aluminium uptake in different tissues. These mechanisms include Tf-mediated endocytosis, uptake via ion channels and active transport mediated by unknown carriers. Data on the aluminium content in different human organs and tissues have been collected by the International Commission on Radiological Protection (ICRP) (58). From this study, it has emerged that the skeleton represents the major part of tissue aluminium, with a percentage around 54%, followed by soft tissues (muscles 14%, adipose tissue 5%, connective tissue 3%, totaling together 22%), skin 13%, liver 3%, gut 2% and brain 1%. Aluminium should be considered as a poison that accumulates in multiple human tissues including bones, causing bone softening and bone mass loss, resulting in osteomalacia with fracturing osteodystrophy.

Many divalent and trivalent metal ions, including aluminium, mainly deposit in the skeleton, and for this reason, these metals are often referred to as bone-seekers (59). Skeletal deposits represent the reservoir for the long-term retention of aluminium within the human body, with half-times being typically 10–20 years (59). The cycle of aluminium in bones starts with the transfer of metal ions from transferrin and citrate in the blood stream to bone surfaces, where aluminium becomes attached. Within the skeleton, aluminium ions are first deposited on bone surfaces, including internal endosteal and external periosteal surfaces, trabecular surfaces and the surface of the vascular channels that permeate compact bones. Subsequently, aluminium ions may be transferred to osteoclasts, large multinucleated bone-reabsorbing cells, or incorporated in the bone matrix. Osteoclasts have been shown to release aluminium to macrophages in the bone marrow. Macrophages could act as a temporary store of aluminium ions, before releasing the metal to citrate and/or transferring the metal ions to other cells, allowing aluminium to re-enter the blood stream (59).

Adynamic bone disease

Aluminium deposits are present at the mineralised bone front on both growing and resting bones. The association between increased aluminium bone stores in dialysed patients and the development of osteomalacia, previously known as 'renal osteodystrophy' has been well established (60). When sufficient quantities of aluminium accumulate, the process of bone formation is disrupted and osteodystrophy (60), subsequently better defined as 'adynamic bone disease' (ABD) (61) or 'aluminium-induced bone

disease' (AIBD), (62) develops. Patients affected by ABD present with spontaneous fractures. Aluminium does not deposit in osteoid, the unmineralised matrix that precedes bone formation and that increases in ABD, but rapidly migrates through it to deposit at the mineralising front, commonly referred as 'lamina limitans.' The presence of aluminium ions at this site inhibits mineralisation of the osteoid matrix, leading to osteomalacia. Aluminium delivered by transferrin to osteoblasts, thanks to the high expression of transferrin receptors on their surface, exerts an antiproliferative effect on osteoblasts, followed by a low bone turnover and osteomalacia (63). ABD has been reported in patients who underwent chronic parenteral nutrition with high aluminium contaminations (64) and in dialysed patients (65). Aluminium-transferrin complexes are also taken up by parathyroid cells, resulting in reduced parathyroid hormone secretion and hypoparathyroidism, which plays a relevant role in the development of ABD (66). Aluminium uptake via transferrin-mediated endocytosis might be linked to the increasing prevalence of ABD in the current dialysis population by inducing a state of hypoparathyroidism (67). Iron status may play a role in aluminium toxicity. In fact, with the introduction of erythropoietin, the dialysis population may have a greater risk of iron deficiency (68), giving an advantage to aluminium in its competition with iron for transferrin (69). The intimate mechanism by which aluminium interferes with parathyroid hormone secretion is not yet clear. *In vitro* studies have shown that cytoskeleton-associated and soluble neurofilament subunits show a marked susceptibility to aluminium exposure (70). Moreover, aluminium has been shown to bind to a number of secretory granule proteins, interfering with the process of exocytosis and, in particular, blocking the release of parathyroid hormone-containing secretory granules (66, 71), causing hypoparathyroidism and ABD.

Brain pathology

Aluminium is unquestionably neurotoxic, as has been well demonstrated in multiple experimental animals and in clinical practice (72). Aluminium deposits in the brain would be of little interest, given their small size and the low impact of the brain upon aluminium metabolism, if it were not for the widely accepted link between aluminium and dialysis-related dementia. The report that some cognition/neuro-behavioural deficits could be associated with an increased aluminium body burden has stimulated research interest (33). Aluminium may enter the brain through multiple routes: from

blood, either through choroid plexus or across the blood brain barrier (BBB) and from the nasal cavity into olfactory nerves, followed by direct distribution into the brain (73). The large size (about 77,000 Da) and low lipophilicity of transferrin preclude its ability to diffuse through the pericellular pathway or endothelial cell membrane (74). The transport both of essential and non-essential metal ions across membrane barriers, such as the blood-brain barrier, is mediated by specific transport mechanisms that regulate the brain levels of different metals (75). These transporters often mediate the uptake of multiple metal ions. Data on tissue aluminium content from patients with chronic renal insufficiency, treated for long periods with dialysis, show high levels of aluminium in the brain, clearly demonstrating the ability of this metal to penetrate the BBB (76, 77). Also, in this case, the intimate mechanisms by which aluminium ions cross the BBB are not well known. About 90% of aluminium in brain extracellular fluid is predicted to be Al-ci and only 4% Al-transferrin (9). As transport of many trace elements, including copper as L-histidine complex, iron by transferrin receptor-mediated endocytosis and mercury as a cysteine complex, has been shown to be carrier-mediated, BBB permeation of aluminium ions cannot solely be attributed to diffusion, and it is probably carrier-mediated as Al-ci (73). Different candidates that may mediate Al-ci transport across the BBB have been proposed. Among them, the best are the monocarboxylate transporter (MCT) and an organic anion-transporting polypeptide (OATP) (73, 78). MCT1 has been found in rat brain microvessels on the luminal endothelial cell plasma membrane (79).

In rats, the half-life of brain aluminium has been estimated at approximately 150 days, which decreases to 55 days in animals receiving desferrioxamine injections (80). These data clearly indicate that aluminium accumulated in the brain can be mobilised by an iron chelator such as desferrioxamine and suggest the existence of a carrier-mediated mechanism to protect the brain from aluminium by effluxing it across the BBB into the blood (73).

Oral exposure of Wistar rats to aluminium chloride for 60 days, apart from producing cholinergic toxicity, has been shown to cause relevant changes in the serotonin system, resulting in a significant increase of 5-HT levels in multiple brain regions (81). Recently, the toxic effects of aluminium on the cholinergic system have been demonstrated in rats. Rats exhibited the typical symptoms of neurotoxicity, including hypokinesia, fatigue and seizures, paralleled by changes in the brain content of the two main constituents of the cholinergic system (acetylcholine and acetylcholinesterase activity)

after the oral administration of sublethal doses of aluminium acetate (82).

Neurological disorders

Aluminium has been implicated in Alzheimer's disease, although the existence of a direct causal dependence has not been demonstrated. The exact mechanism of aluminium toxicity on brain cells is not known, but there are several lines of evidence showing that this simple trivalent cation, incapable of redox changes, might exacerbate oxidative events and activate reactive oxygen species generation, linking aluminium storage to the pathogenesis of Alzheimer's disease (44).

The hypothesis that aluminium might exacerbate events associated with neurodegenerative diseases, and in particular Alzheimer's disease progression, is clearly emerging. The role of aluminium could be related to its ability to potentiate iron-induced oxidative events, increasing the formation of reactive oxygen species. Moreover, accumulating evidence suggests that aluminium potentiates inflammatory events by inducing the synthesis and/or release of interleukins and other inflammatory cytokines (83). The controversy about the role played by aluminium in the pathogenesis of Alzheimer's disease has existed for many decades, but the question of whether aluminium represents a health hazard and whether it plays a relevant pathogenetic role in the development of Alzheimer's disease is still the subject of debate. Two key questions that must be answered before a causal relationship can be stated between aluminium exposure and Alzheimer's disease have been addressed by Savory et al. (72):

- Is aluminium content elevated in the brain of AD patients?
- Is it possible to demonstrate a strict relationship between aluminium exposure and an increased risk of AD?

Regarding the intimate mechanism of aluminium overexposure and Alzheimer's disease progression, even though aluminium only exists in the trivalent form and it is redox-inert, this metal ion has been shown to interact with transition metals such as copper ions in the promotion of oxidative events. This synergistic interaction increases copper-induced reactive oxygen species production, oxidative cell stress and cell death, adding a new piece to the puzzle of the multifactorial aetiology of Alzheimer's disease (54). Moreover, an important role in the neurotoxicity played by aluminium ions has been recently related to their ability to interact with copper ions

at a subcellular level. According to this hypothesis, the interaction between aluminium and copper, both present in trace amounts in drinking water, could initiate and propagate an inflammatory response in the ageing brain, participating in the neuroinflammation reported in the brains of Alzheimer's disease patients, eventually inducing or potentiating neurodegeneration and boosting the progression of dementia (84). Evidence for the participation of aluminium in the formation of neurofibrillary tangles, a histological marker of degenerating neuronal cells in patients affected by Alzheimer's disease, have been recently obtained in hippocampal pyramidal cells from brains of aged humans with Alzheimer's disease. In this experiment, a portion of neurons contained short filaments, suggestive of early neurofibrillary tangles, which proved to be aggregates of an aluminium/hyperphosphorylated tau complex, supporting a role for aluminium in the formation and growth of neurofibrillary tangles in Alzheimer's disease (85). Even though many Alzheimer's disease animal models have been utilised for better understanding the role of aluminium in the origin and progression of the disease (86), the neurotoxicity and the role of this metal in AD is still considered an issue (87). In models with animals treated with aluminium at low doses, reflecting those found in some water supplies, aluminium salts were able to increase levels of glial activation and inflammatory cytokines, favouring the appearance of excess levels of brain inflammation, which suggests the hypothesis that aluminium could act as a subtle promoter by accelerating some characteristic indices of brain ageing (87).

The following factors have been proposed in favor of a strict correlation between aluminium exposure and AD progression: the abundance of neurotoxic aluminium on earth and its bioavailability to humans; only small amounts of aluminium are needed to cause neurotoxicity; the ability of aluminium ions to cross the BBB; and the experimental evidence regarding neuronal death caused by aluminium intoxication (88). However, oral intake of aluminium in mice did not accelerate progression of brain pathological changes typical of Alzheimer's disease, contradicting the notion that excessive oral intake of aluminium is a risk factor for AD (89). Moreover, oral exposure to aluminium in mice did not alter recognition memory and did not accelerate the deposition of beta-amyloid plaques (90). In a recent review on the effects of chronic exposure of the human brain to aluminium ions, the ability of aluminium ions to substitute essential metals such as Mg^{II}, Fe^{II} and Ca^{II} ions in intraneuronal proteins was underlined. On the basis of these data, the author hypothesised that aluminium might disrupt calcium homeostasis in human neurons with remarkable signal transduction changes, as

frequently observed in Alzheimer's disease patients (77). The intimate mechanism of aluminium-induced neurotoxicity has been recently linked to the accumulation of iron and to the production of reactive oxygen species, suggesting that aluminium-induced neurodegeneration could be halted by chelating excess iron (91).

Aluminium and the Gulf War syndrome (GWS)

Previously described as chronic fatigue syndrome (92), Gulf War syndrome (GWS) is a multisymptom condition described in a significant percentage of USA veterans of the 1991 conflict known as the Gulf War who, months after their return home, experienced muscle fatigue associated with impaired cognition, ataxia, diarrhoea, bladder dysfunction, headache, arthralgia, skin rashes and sleep disturbances (93). A subset of veterans of the 1991 Persian Gulf War developed a severe motor neuron disease, virtually indistinguishable from classical amyotrophic lateral sclerosis (ALS), except for the age of onset (94). Whereas numerous environmental factors have been linked to the origin of GWS, the role of the adjuvant aluminium hydroxide associated to the multiple vaccines that Western army soldiers underwent during the months before their departure to the Persian Gulf War has come under increasing scrutiny (95). Recently, GWS, together with other syndromes linked to previous exposure to

an adjuvant, including macrophagic myofascitis syndrome (MMS) (96), siliconosis and other post-vaccination adverse effects, have been included in the autoimmune/inflammatory syndrome induced by adjuvants, the ASIA syndrome (97).

Conclusions

Taken all together, these data clearly indicate that aluminium represents a significant component of exposure of humans to xenobiotics and contaminants and that newborns are at risk of aluminium-related toxicity not only in the perinatal period, but also in childhood and in adulthood. To alert the medical community about the risk humans are experiencing from aluminium exposure represents an ambitious but measured plan that could be initiated, extending with caution information to pregnant women and to mothers about the vulnerability of infants to early exposure to this contaminant. Moreover, food manufacturers should be forced to indicate on labels the level of aluminium contained in every food product, with particular care for neonatal products, to reduce aluminium-related human pathologies, with the hope of halting the epidemic increase of neurodegenerative diseases in elderly people.

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