Aluminium – A Potentiator of Multiple Evils

Aluminium (Al) is omnipresent in the environment as well as plant and animal tissues. Instead of ubiquitous and adequate (nearly 8% of the earth’s crust) presence of it, no useful involvement of the metal, either in ionic or complex form, is reported in the life processes. On the other hand, all the vital organs or systems are vulnerable to toxic impacts of Al in some or other conditions. When a good number of rare elements even have some physiological roles in lives, it is unique that the evolution has bypassed this highly reactive and abundant element. As if, the biological system has ignored the presence of Al in the environment. Hence, there is no dedicated or shared cellular mechanism(s) for the entry and, quite understandably, the exit of Al across the cell membranes. While restricted entry rendered benefit of limited internalization of Al despite environmental copiousness, the threat of its toxicity is enhanced by extra-ordinarily prolonged half-life of that Al which reached the cell interiors by some means.

Even in presence of 75% recyclability, the production and consumption of Al has increased exponentially. Till date, nearly a billion tonnes of Al has been produced globally. Considering these facts, one can easily approximate the increasing load of Al constantly added to the environment and biota. A major share of naturally occurring Al remained unavailable to biological world; however, anthropogenic acquisition processes perpetually enhanced its environmental availability. High concentration of Al in the surroundings facilitate the probability of gaining access inside the biological barriers by competing with other cations or other unusual means.

Unparallel physico-chemical properties of Al allowed it to be used in every sphere of life and literally, we are living in the ‘Age of Aluminium’. Starting from daily-use household amenities to public and industrial large-scale uses made exposure to Al unavoidable. In addition, considering it as ‘biologically inert’, Al finds its place in many eatables and drinkables as additive or preservative. The worst part is use of Al in the common food items for commercial and decorative purposes only. Similarly, avoidable use of Al is also common in commercially available nutrient supplements for infants and otherwise compromised patients. Even medicinal use of Al-salts as antacid, irrigant, binder, emetic, adjuvant and cosmetic uses of Al-salts as astringent, antiperspirant, deodorant enhanced its exposure multifold for the users. Apart from these dietary, environmental and iatrogenic exposures, some professionals face additional exposures in their workplaces as in metal refineries, automobile industries, etc. Use of Al-contaminated fluids for intravenous administration or Al-salts as adjuvants in vaccines can be the cause of superfluous systemic Al burden as it is bypassing the protective mucosal / dermal barrier and have direct access to the extracellular fluids. Recently, concerns have been expressed with use of Al-salt nanoparticles, however, no comparative report is available claiming worse effects of them over regular Al-salts micro particles. Surprisingly, even though Al-salts are common in foods (preservatives, additives, contents), and, Al is used in its metallic form for packaging, cooking, storing and serving of food items, assimilation of Al from dietary exposure is only insignificant in physiological conditions. On the other hand, use of Al-embellished food ingredients or preparations and drinks as nutritional supplements or consumption of acidic or basic food materials stored in Al utensils or containers can augment the risk of Al exposures.

Serum Al level is in dynamic flux. Normally, the serum level is maintained within the tolerable range. Elevation of serum Al level is possible in individuals with circumvented gastrointestinal barrier or compromised
urinary and/or hepatic elimination. Even in the presence of very slow and limited process of internalization, sluggish accumulation of Al happens in some organs with unequal distribution. Bones, liver, brain, are the major sites of Al accumulation. Lungs also join the list, particularly in the case of inhalation exposure. Skin, lower gastrointestinal tract, lymph nodes, adrenal, parathyroid glands are also known target organ for Al accumulation. In the long run, with aging, these organs may lead to development of some tardive clinical symptoms. Interestingly, no specific clinical symptom is associated with Al exposure, except in very high dose acute toxicity. It causes only subtle slow changes in the physiological processes, which normally do not provide any sense of discomfort or pain and hence remain unnoticed.

Even in the absence of direct evidence to implement Al in the pathogenesis of Alzheimer’s disease (AD), its causal role has been suggested because of - (a) presence of Al in AD brains, (b) AD-like pathology in Al-intoxicated brains, and (c) epidemiological association between Al exposure and risk of AD. Chronic progressive neurodegenerative changes in brain, upon exposure to Al, made it to be associated with a number of other CNS diseases. Neurotoxicity is the most studied and highlighted effect of Al in human and animal studies. Numbers of neuropathological conditions have been associated with Al exposure and its presence in neuronal tissues. Premature senility and neurodegenerative changes are the hallmarks of Al toxicity. However, it has been also entailed with male and female infertility, non-iron-deficient microcytic anemia, dyslipidemia, endocrine disorders, osteomalacia and breast cancer. Cardiotoxicity and hepatotoxicity are also reported in experimental setups. On the other hand, the Al-induced neurotoxicity first came into the limelight in patients with compromised renal functions particularly those received dialysis with Al as phosphate binders.

Mechanism of Al toxicity is an unsolved riddle till date. Possibilities of Al’s toxic impact in brain include altered genetic cross-talk and expression, amyloidosis, disruption of Ca\(^{2+}\) and other cell signalling processes, excitotoxicity, interactions with biomolecules, up/down regulations of matrix metaloproteinases, membrane transport malfunctions, along with metabolic alterations leading to dyslipidemia and energy-hindering mechanisms. In addition, Al can cause activation of glial cells and microglial cells and these in turn can cause the toxic impact on neuronal cells. Among these, oxidative stress and inflammation are the most widely proposed molecular connections between presence of Al and its toxic impacts on any organ. While oxidative stress is the commonest phenomenon in any type of Al intoxication in all types of tissues, the source of oxidative stress is still undecided. Considering the redox inactivity of Al\(^{3+}\), it is very unusual that oxidative stress can be created by the Al itself. A number of redox-active molecular couples have been suggested to be involved in the process of Al-induced oxidative stress. Even, some types of Al-superoxide species are also proposed to explain the process. Nevertheless, failure of exogenous antioxidants to prevent the molecular and behavioral toxicity in experimental setup doubted the involvement of oxidative stress in the pathogenesis of Al-induced neurotoxicity.

In the absence of evidence for any direct interaction between Al and biomolecules, deracination of essential elements by it is widely explored area. Because of closely similar atomic properties, Al is a possible interloper for iron-protein interplay. Involvement of iron in the Al toxicity is hypothesised for reported oxidative stress in experimental studies. Derangements of serum levels of copper, zinc, calcium, magnesium, etc. are common for those faces long-term industrial Al exposure. Reported microcytic anemia, amyloidosis and osteoporosis in Al toxicity may arises from its interactions with iron, copper and calcium, respectively. However, these impacts of Al are modifiable and highly depends on the related endocrine status.

Reports about Al’s ability to interfere with estrogen functions are available for few decades. Recently these reports came into the limelight. Along with its genotoxic and possible carcinogenic activities, Al is now held responsible for the breast cancer. Furthermore, the anti-estrogenic pathway is being explored for its role in
neurotoxicity. Even, the link between Al-associated oxidative stress and estrogenic status of the subject has also been suggested.

A perpetual state of inflammation is common in brain, muscle, gastrointestinal tract when they face the exposure to Al and particularly in the presence of other pro-inflammatory factor(s) or conditions. While neuroinflammation has been proven to be involved in the Al-induced cognitive deficits, inflammatory changes in kidney and liver are observed in experimental setups of Al exposure. Positive correlations between serum Al and serum levels of pro-inflammatory cytokines in some clinical conditions are also reported, however, negative reports are also not sparse. Exposure of neonates to Al in the form vaccine adjuvants as part of national health policy is being questioned because of its possible involvement in the development of macrophagic myofascitis and autism. In both types of cases, presence of chronic inflammation is undeniable, and evidences are suggestive of association with Al exposure through vaccinations. As intestine is the major organ which face maximum exposure to Al through dietary burden, a growing number of inflammatory conditions of the intestine, like Irritable Bowel Syndrome, Cholitis, Crohn’s Disease, Inflammatory Bowel Diseases, indicating an association between these. Interestingly, in most cases Al is suggested to be an appurtenant not as causative; as it was observed in case of oxidative stress. However, intermediaries of oxidative stress pathway can also influence the cytokines and take part in the inflammatory pathway.

Even though, Al causes grievous health problems; it remains mostly unrecognized to the medical fraternity because of lack of specific symptoms of Al toxicity. For some western countries maximum tolerable limits have been identified; however, there is no guideline in India about the use of Al even in edible and drinkables. Even, there is no data regarding the level of Al in the environment and natural resources.

Once well-known as neurotoxin, Al’s roles have been identified in a wide spectrum of health issues and disease processes. Even then, the only option available is to avoid Al exposure, as the mechanism of Al’s interference with cellular process is still unclear. With continuous environmental loading of Al and widest possible application in every sphere of life, avoiding exposure to Al is next to impossible. Clinical, epidemiological and environmental research are therefore necessary to unfold the molecular pathways to Al-induced alterations and means to overcome them. Though a great deal of work has been already carried out, the number of published reports regarding perniciousness of Al is gradually coming down. This is mostly because of equivocal reports of Al’s role towards human morbidity. Nevertheless, lack of awareness about its presence or interference in the clinical scenario is also responsible for this withdrawn attention by the researchers toward this disastrous element. A number of animal models have been developed initially only to mimic Alzheimer's disease by exposing them to a variety of Al salts and exposure routes. Now it is more important to study the effects of Al exposure itself, in addition to using these animal studies as models for neurodegenerative diseases. Studies exploring Al’s role in endocrine disorders including common reproductive health concerns for women, osteoporosis, unexplained anemia, dislipidemia, gastrointestinal problems, breast cancer, sporadic neurodegenerative diseases are needed with special emphasis towards the possibilities of Al exposures. Uses of Al in daily life is increasing gradually. In this situation, drives should be initiated to explore the Al’s involvement in a variety of pathophysiological processes, particularly in the case of unsolved riddles. Neurotoxin Al may hasten the development of neuropathies associated with other pathological conditions or chronic toxicities. On the other hand, Al as metabolic interrupter can be involved in obesity, diabetes as well as in dyslipidemia. Therefore, Al’s contribution in the rising incidences of metabolic syndrome should also be evaluated. Presence of Al can worsen reperfusion injury and post-stroke incidents or rehabilitation processes as well. Thus, a myriad of unexplored areas are there to understand the overall health burden caused by uncontrolled use of Al. With the introduction of nanoparticle forms in various uses of Al, the risks are likely to increase significantly. However, no systematic evaluation of these aspects of Al exposure and scaling of impacts has been carried out.
Being an unrecognised assailant, very few efforts have been made regarding the detoxification procedure for Al-intoxicated individuals. Removal of Al or countering its effects could be an area for upcoming research. National level campaign for awareness about the health concerns of excessive Al exposure, avoiding Al as much as possible and use of alternatives should also be initiated.

**Prasunpriya Nayak**

Associate Professor  
Department of Physiology,  
All India Institute of Medical Sciences  
Basni, Phase II, Jodhpur  
Rajasthan – 342 005. INDIA