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Editorial

Aluminum Should Now Be Considered a Primary Etiological Factor in Alzheimer's Disease

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Abstract. In this paper, I have summarized the experimental and largely clinical evidence that implicates aluminum as a primary etiological factor in Alzheimer's disease. The unequivocal neurotoxicity of aluminum must mean that when brain burdens of aluminum exceed toxic thresholds that it is inevitable that aluminum contributes toward disease. Aluminum acts as a catalyst for an earlier onset of Alzheimer's disease in individuals with or without concomitant predispositions, genetic or otherwise. Alzheimer's disease is not an inevitable consequence of aging in the absence of a brain burden of aluminum.

Keywords: Aluminum, Alzheimer's disease, brain aluminum, environmental factors, genetic predisposition, human health

EVIDENCE NOW POINTS TO ALUMINUM AS A CONTRIBUTORY FACTOR IN ALL FORMS OF ALZHEIMER'S DISEASE

Aluminum is unquestionably neurotoxic [1] and it is accepted as the cause of encephalopathies in, for example, individuals undergoing renal dialysis [2] and similarly in individuals who have received aluminum-based prostheses [3]. There are myriad ways by which aluminum can exert toxicity; its $Al^{3+}_{(aq)}$ ion is highly biologically reactive, but to do so and thereby bring about change in a biochemical system, the aluminum content of any compartment, such as a tissue, must achieve a toxic threshold or burden [4]. However, aluminum-induced encephalopathies are not Alzheimer's disease, though they may share some similar neuropathological hallmarks [5]; they are acute conditions whereas Alzheimer's disease might now be considered as an acute response to chronic intoxication by aluminum [1].

WE DO NOT KNOW WHAT CAUSES ALZHEIMER'S DISEASE

While the causes of Alzheimer's disease remain unknown, we do know that the neuropathology of Alzheimer's disease, if not the disease *per se*, and specifically in relation to the deposition of amyloid-β and tau can be reproduced in transgenic animal models [6]. We also know that the addition of aluminum to feed or water exacerbates the many symptoms of Alzheimer's disease in these animal models [7, 8].

WHAT ARE THE PERTINENT RISK FACTORS FOR ALZHEIMER'S DISEASE?

In the majority of individuals, aging is perhaps the single most important risk factor for the development of Alzheimer's disease [9] and similarly, aging is also the most critical criterion in the

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accumulation of aluminum in human brain tissue [10]. Neurons have been described as the 'quintessential immortal cell line', and it is their longevity which predisposes them to accumulate aluminum over time [4]. There are various intraneuronal pools, for example, citrate, ATP, glutamic acid, and the nucleic acids of the nucleus, where aluminum could remain benign and accumulate over time before at some point the biologically-reactive $Al^{3+}_{(aq)}$ exceeds a critical threshold and begins to exert toxicity [10].

Mutations in the metabolism and processing of the amyloid-β protein precursor (AβPP) and related biochemistry are significant risk factors for Alzheimer's disease [11, 12]. These genetic predispositions form the basis of a diagnosis of familial Alzheimer's disease which is invariably an early onset form of the disease. We have recently completed the first ever study on the aluminum content of brain tissue from donors who died with a diagnosis of familial Alzheimer's disease [13]. The data, supported by complementary imaging using fluorescence microscopy [14], revealed some of the highest concentrations of aluminum ever measured in human brain tissue. These seminal findings suggest that AβPP and mutations associated with its metabolism and enzymatic processing predispose individuals to a more rapid accumulation and/or longer retention of aluminum in brain tissue. For example, one or more of these mutations may result in the enhanced absorption of aluminum across the gastrointestinal tract in individuals with familial Alzheimer's disease, as has already been shown in individuals with Down's syndrome (Trisomy 21) [15] and individuals with late-onset or sporadic Alzheimer's disease [16]. We know that within the non-Alzheimer's disease population that there can be an order of magnitude difference in the gastrointestinal absorption of aluminum [17]. Similar differences may also exist in the excretion of aluminum from the body and these differences may be genetically determined and may even be related to the metabolism and/or processing of AβPP and its numerous metabolic products including amyloid-β.

There are occasional cases of Alzheimer's disease with an early onset, for example, individuals in their fifties, where there are no known genetic predispositions. We have described several such cases in which the affected individuals had been subjected to environmental [14, 18] or occupational exposure [19] to high levels of aluminum over extended time periods. Postmortem analyses of their brain tissues revealed very high levels of aluminum. In these cases of early onset and particularly aggressive Alzheimer's disease, without any known genetic predispositions, it was concluded that it was inevitable that aluminum contributed to disease etiology.

WHAT PROTECTS AGAINST ALZHEIMER'S DISEASE?

While we do not know the cause of Alzheimer's disease and we do not have any effective therapies to treat the disease, there are a number of 'environmental' indices which are known to influence the incidence and progression of Alzheimer's disease. For example, the incidence of Alzheimer's disease is higher in females [20] and the onset and progression of Alzheimer's disease may be delayed by physical exercise [21]. Aluminum as an etiological factor in Alzheimer's disease links the two in that perspiration is a major route of excretion of aluminum from the body [22]. In the absence of physical exercise, women produce only half the volume of perspiration as men and so may be predisposed to the retention of aluminum in their tissues. In both sexes, physical exercise can increase the perspiration volume many times and so improve the excretion of aluminum from the body. Could exercise-induced improvements in the excretion of aluminum from the body be significant in the benefits of exercise in Alzheimer's disease?

Epidemiological data have been equivocal in establishing a relationship between the aluminum content of drinking water and the incidence of Alzheimer's disease. However, research has shown a significant protective effect of silicon in drinking water, irrespective of the aluminum content, with higher silicon reducing the incidence of Alzheimer's disease [23]. In addition, clinical trials involving only a small number of participants have shown that regular drinking of a silicon-rich mineral water helps to remove aluminum from the body of individuals with Alzheimer's disease [24, 25]. For 20% of such individuals, the lowering of the body burden of aluminum following drinking a silicon-rich mineral water for just 12 weeks produced clinically significant improvements in their cognitive function [25]. The potential benefits of silicon in Alzheimer's disease can only be explained if aluminum has a role to play in the disease.

SUMMARY

Aging is the major risk factor for Alzheimer's disease though the advent of Alzheimer's disease within

a normal human lifespan is suggested to be brought about through human exposure to aluminum. Essentially without aluminum in brain tissue there would be no Alzheimer's disease. There are a number of predispositions to the development of Alzheimer's disease, involving both environmental and genetic factors, and each of these acts to increase the aluminum content of brain tissue at specific periods in an individual's life. This interplay between environmental and genetic factors explains both early and late onset disease, in each case the catalyst for the disease is always the brain aluminum content and how robustly an individual's brain responds or copes with this aluminum burden.

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