

Commentary

Aluminum and Alzheimer's disease: A *Vexata Questio* between uncertain data and a lot of imagination

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1. Introduction

In this commentary, I express my opinion regarding the *Vexata Questio* of Aluminum and Alzheimer's disease (AD) concomitantly with the publication of the paper by Exley et al. [13]. First of all, in my opinion, the title of the Exley paper is conceptually inappropriate when it refers to a "Non-invasive therapy" using mineral water containing silicon and other elements. Drinking mineral water is always a positive thing, but is far removed from the concept of therapy (from Greek *Therapeia*, a service done to the sick). I would suggest the more appropriate term "supplement, supplemental".¹ The mineral water utilized by Exley and colleagues contains other mineral elements besides silicon (e.g., Mg^{2+}) which could also influence the effect observed by the authors. In this connection, it is important to bear in mind the "**domino effect**", i.e., the effect produced by modifying the uptake or the metabolism of one single element as the cause for the alteration in the physiological distribution, concentration, and excretion of several other elements, and, in this case, most likely not only aluminum.

The paper by Exley and colleagues reminds me of an old story based on an idea pursued years ago by

Prof. Derek Birchall [6–8], an unforgettable friend, a pioneer in the study of silicon and the mentor of Chris Exley (see [4]). In his paper, Birchall and colleagues demonstrated that individuals given monosilic acid as naturally found in beer, excreted the majority of the silicic acid content within 8 hr, concomitantly with a significant increase of aluminum excretion. Excretion of aluminum reached a peak and then declined, consistent with the depletion of aluminum body stores, and confirmed by using aluminum isotope as a probe [26]. Data seem to indicate that silicon counteracts aluminum adsorption rather than removing the toxic metal ions from tissue or even, with a pinch of imagination, from the brain. Other authors reported similar findings with the ingestion of 0.6 L of beer (22.5 mg silicon and 4.6% v/v ethanol) where silicon excretion increased considerably [26]. Just a curiosity: the English and the Germans drink respectively about 6.5 and 9 times more beer than Italians every year, and thus take in different supplementation of silicon; but apparently there are no effects on incidence of AD observed in these countries. By the way, drinking beer should be "therapeutic", more pleasant than drinking mineral water.

Next to oxygen, silicon is the most abundant element on the Earth's crust. The human body contains approximately 7 grams of silicon, which is present in various tissues and body fluids; it is usually bonded to glycoproteins e.g., in the cartilage. In the blood of

¹Serving as a supplement or addition. Medical Dictionary, Dorland's Illustrated 27th ed. (1988) W.B. Saunders Co, Philadelphia.

normal subjects [5] with normal renal function, silicon is under $100 \mu\text{gL}^{-1}$ and more than that in the presence of renal dysfunction [29]. Dietary intake is the main source of silicon for humans. Cases of silica stones and renal silica calculi have been reported as ascribed to the silicate-rich mineral. The occurrence of silicon dioxide in human urinary calculi has been known for a long time and is more common than generally believed [3]. Furthermore, as regards the correct intake of food and beverages several hypotheses/proposals have been advanced on the beneficial effects of a "correct" diet for helping a better aging and to prevent AD. I recall for instance the so-called **Mediterranean diet**, rich in legumes, fruit, vegetables, and cereals (particularly rich in silicon), rich in all mineral elements, antioxidants, phytohormones and fibres, virgin olive oil [20] and red wine, also full of minerals and antioxidants like resveratrol [15,20].² A good diet certainly may help people to live better and age better, but I am rather sceptical about it being a cure for complex diseases like AD that are certainly multifactorial in character and still etiopathogenically obscure 100 years after its first description (this year marks the centenary).

But let me start my comment with a broader approach, because here we are dealing with a very serious problem like the possible, not yet demonstrated, connection between aluminum and AD. A thousand papers and perhaps a hundred books have been published on this issue, including those published by my laboratory with more than 25 years of research in this field, trying to shed some light on this complex topic, but the dark still reigns sovereign. Nowadays, besides speculations and fanciful hypotheses, nobody has the facts to be able to state that aluminum is the cause of AD. However, I am convinced that the aluminum-AD hypothesis is still a rather open issue, even if we are, as it were, navigating in dense fog without a compass. So far it is totally unclear if metal accumulation is the first or the secondary event, whether it is pivotal in driving the progression of the disease, and how it may interact with genetic factors. In addition, one of the major sources of confusion in the field of aluminum toxicity is that authors very rarely distinguish the concept of **aluminum neurotoxicity** from that of **neurodegeneration**. While the former has been well demonstrated for aluminum, the latter has only been faintly ascertained. The understanding of mechanistic analogies and differences

among toxic and non-toxic diseases deserves more attention, in that it may help to clarify the role of metal accumulation in neurodegeneration.

Aluminum toxicity, mainly in experimental animals, was demonstrated in 1800. However, as most readers will remember, the "**Aluminum Affair**" [11,12] in humans began when Prof. Allen C. Alfrey described for the first time dialysis encephalopathy (Aluminum dementia) as an abnormal accumulation of aluminum in the brain mass of uremic patients with renal failure undergoing chronic dialysis, when tap water, without any kind of purification, was utilized in the dialysis process. Aluminum was, and still is, largely used in drinking water flocculation procedure. Once the aluminum was eliminated from the "dialysis bath", the aluminum encephalopathy practically disappeared, removing the etiopathogenic factor [2]. Nowadays, nephrologists know that the best way to decrease the hyperphosphatemia in uremic subjects is to use aluminum salts; in fact aluminum is used in this connection by 50% of nephrologists, while the other 50% are most likely being "economical with the truth" when they say they do not use aluminum. In spite of this consolidated practice for several decades, there is no major incidence of AD in uremic patients in chronic dialysis with respect to the normal population. Thus, there must be another reason for AD besides the presence of aluminum.

Aluminum powder exposure at high concentrations may give rise to fibrosis of the lung (**aluminosis**). Finely ground aluminum and aluminum oxide (*McIntire power*) was largely used as a prophylactic agent against silicosis between 1944 and 1979 to treat gold miners in Northern Ontario. Ten years after treatment, Sandra Rifat et al. [24] showed that there were no significant differences between treated and non-treated workers in terms of reported diagnosis of neurological disorders. However, the treated miners performed less well on cognitive state examination. The authors concluded that chronic aluminum exposure produce a putative neurotoxic (not neurodegenerative like in AD) effect.

Aluminum levels in the total brain mass from AD subjects and in relevant controls showed no differences. However, several papers have reported, with controversial results mainly due to inappropriate analytical approach, high aluminum concentration in the senile plaques and neurofibrillary tangles (NFT) in AD [30]. More recently, a well-known laboratory, with an indisputable international reputation in the field of analytical inorganic chemistry, measured the level of aluminum concentration in several areas from autoptic brains from

²Resveratrol is a substance produced by several plants and present in wines (mainly red) and concurring to justify the still undemonstrated "**French Paradox**".

AD subjects with NFT and in comparison age-matched controls. They concluded that aluminum accumulation in AD brains is small and generalized in both NFT-free and NFT-bearing neurons, and the difference appeared to be significant ($p < 0.05$, analysis of variance) [17]. On the other hand, the same authors analysed the senile plaques (rim and core) from AD and found that copper was significantly higher ($p < 0.05$) in the rim of senile plaques compared to AD neuropil where zinc was also observed to be higher with respect to a neuropil-control [18]. But copper and AD is another story very similar to the aluminum hypothesis but without factual substantiation so far. Silicon and aluminum have been found to be co-localized in *cores* isolated from senile plaques of patients with senile dementia, in the *cores* studied *in situ* from tissue sections from the cerebral cortex of pre-senile, and senile patients with AD, and elderly, mentally normal subjects [9]. The role of aluminosilicates in senile plaques [28] has never been explained and the chemistry of aluminosilicates formation is far from being fully understood in biological systems [16].

In the west of England in 1988, 20 tonnes of aluminum sulphate were accidentally introduced into the water treatment unit that was to be pumped to a village's 20,000 inhabitants. This serious accident caused a large number of scientists to study this unique case. Recently, **one case report** dealt with a woman exposed at 44 years of age to the Camelford accident who died 14 years. The aluminum content in her brain was shown to be similar to that observed in aluminum encephalopathy [14]. The autopsy revealed some amyloid- β positivity also present in the histology of AD brains but not specific to this disease, since it is well known that such a positivity can also be found in the plaques from subjects without neurological disorders. In connection with this study Professor Daniel Perl of Mount Sinai School of Medicine, who has been one of the pioneers for 30 years in the study of aluminum-hypothesis [22], points out that the association between an increased risk of AD and exposure to aluminium is somewhat controversial, largely because there are few epidemiological data to support the theory. In addition, recently Prof Enrich Reusche [23] from the University of Lübeck, Germany reporting a study on 50 haemodialysis patients stated "*it has been clearly shown that aluminum does not cause an increase in the morphology of AD, at least in terms of drugs or haemodialysis*", establishing once and for all that "*the morphologies of AD and dialysis encephalopathies are completely different*." His conclusion is that there is no room for speculation on this count.

In a recent epidemiological report [25] studied different sources of aluminum exposure such as occupational, aluminum-containing products, with emphasis on drinking water. They divided the various health effects of aluminum into three categories: neurological disorders (other than cognitive decline or AD); cognitive decline; and dementia/AD. They also presented the results obtained on silicon in drinking water, a chemical constituent that interacts with aluminum. The authors concluded that not enough epidemiological evidence supports a link between aluminum in drinking water and AD. The role of silica in drinking water has been studied less, and clear results have not yet emerged.

Data on aluminum excretion in humans are very scarce, as Exley and colleagues also report in their paper. In one of the very rare studies in this connection, Morie et al. [19] described how aluminum excretion in AD patients tended to be higher than that of an age-matched healthy group. However, in this study some AD patients were under antacid treatment and it is also reported, as is well known, that they are unable to control their urination, making it difficult to collect urine from AD patients over a period of 24 hr, bearing in mind that aluminum excretion in urine changes in the course of the day. This is also a criticism of Exley et al.'s methodology, in that they used urine "spot collection" without a valid justification, instead of 24 hr sampling. The analytical consequences of these kinds of studies, if not properly controlled, are inconclusive. Thus, to the best of my knowledge, we still do not know whether AD patients' excretion is really a general phenomenon among age matched controls without neurological disorders.

2. Conclusions

1. Aluminum when present in the body at high concentrations causes a variety of diseases, toxic in character (e.g., microcytemia non iron-dependent, osteomalacia and others). These are mostly reversible when the toxicant is removed, as in dialysis encephalopathy. All these effects have been well described mainly in uremic subjects where they commonly occur, or in particular cases of aluminum pharmacological intoxication [31]. At low concentrations aluminum causes no measurable effects.
2. At the beginning of the **aluminum-AD hypothesis**, aluminum was proposed as the major etiological factor in AD [11,12]. But after 30 years of

- studies, it appears that aluminum may be only a possible co-/aggravating factor, with no convincing proof available so far.
3. Previous experiments with silicon supplementation in rats have demonstrated that no significant silicon amount was detected in the brain after ^{31}Si silicon supplementation [1].
 4. In spite of the analytical presence of aluminosilicates in the core of plaques from AD and non mentally effected subjects, nobody has demonstrated either the positive or negative role of silicon in relation to AD. In this connection, 20 years ago one of the major scientists in the study of AD, Prof. Robert D. Terry [27] stated: “*the Aluminum silicate story has been a very elusive one in terms of proof or even confirmation*”. Nobody has been able to produce evidence to contradict this statement.
 5. One of the major causes of aluminum toxicity is its ability to displace Mg^{2+} from key sites at which this metal is catalytic [7]. Thus in order to interfere with aluminum adsorption a more plausible and reasonable way, in terms of supplementation, is to utilize Mg^{2+} (and Ca^{2+} with kidney functioning perfectly) to compete with aluminum, not only at the absorption level. It is important at this stage to recall that hypomagnesaemia occurs rather often with aging concomitantly with a reduced efficiency of the gastrointestinal protective function, low magnesium content in the diet. This pathophysiological aspect stresses the importance of magnesium supplementation in the elderly with or without AD. Furthermore, and differently from silicon, besides contrasting aluminum storage, magnesium is involved in several hundred enzymatic reactions, many of which contribute to the production of energy and cardiovascular functions. Diuretic drugs, often used in hypertension, relatively common in the elderly, causes magnesium depletion, as do alcohol, caffeine, and sugar. Decreased blood and tissue levels of magnesium have been shown to be related not only to high blood pressure, but also kidney stones, heart disease and, particularly, heart attacks due to coronary artery spasm. Again, magnesium helps relax and dilate coronary arteries, bearing in mind that coronary and, more generally, blood vessel rigidity is a consequence of aging and is commonly present in AD subjects.

6. Because the actions of supplemental silicon is not known, personally I would not recommend silicon supplementation as it was not recommended several years ago by other authors (e.g. [21]).

In my modest opinion, the paper by Exley and colleagues needs serious reconsideration not only as a practical idea to pursue, but also because of its very weak methodological approach and its poor and inconclusive statistical analysis.

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