Journal of
Alzheimer's Disease & Parkinsonism

Ohyagi and Miyoshi, J Alzheimers Dis Parkinsonism 2013, 3:2
DOI: 10.4172/2161-0460.1000118

Review Article Open Access

Aluminum and Alzheimer's Disease: An Update

Yasumasa Ohyagi[1]* and Katsue Miyoshi[2]

[1]Department of Neurological Therapeutics, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan
[2]Department of Neurology, Kushiro-Kita Hospital, Kushiro 084-0902, Japan

Abstract

Alzheimer's disease (AD) is the most common form of dementia in the elderly. AD is characterized by senile plaques and neurofibrillary tangles (NFTs) comprised of amyloid-β protein (Aβ) deposits and hyper-phosphorylated tau protein (p-tau), respectively. Oxidative stress-induced neuronal damage is also involved in AD pathogenesis. In the 1970s, studies showed increased levels of aluminum (Al) in the AD brain, and neurofibrillary changes upon its injection into the brain, thus leading to the suggestion that Al may be one of the major causes of AD. However, later reports contradicted this hypothesis as studies revealed that Al-induced neurofibrillary changes were different from NFT sin AD, and intake of high dose Al-containing antacid drugs did not induce AD. Other *in vitro* and *in vivo* studies found that Al was neurotoxic, and possibly promoting aggregation of Aβ and p-tau. Here, we review and verify the validity of Al pathogenesis in AD. Despite the multitude of studies, no direct evidence currently exists that specifically links Al with AD pathogenesis. Therefore, more advanced cohort studies are necessary to better understand the absolute risk of Al for AD, and to rigorously compare this link using other neurotoxic metals. Taken together, Al may be an environmental factor promoting cognitive impairment in AD patients, as well as other free radical-generating metal ions such as iron, copper and zinc.

Keywords: Alzheimer's disease; Aluminum; Dementia; Oxidative stress

Introduction

Alzheimer's disease (AD) is the most common form of dementia, mainly occurring in the aged population (>65 years of age). Pathologically, AD consists of two major hallmarks: neurofibrillary tangles (NFTs) and senile plaques (SPs), which are comprised of hyper-phosphorylated tau (p-tau) filaments and amyloid-β protein (Aβ) fibrils, respectively. Numerous reports suggest that Aβ aggregation, namely the formation of Aβ oligomers, is an early event preceding other pathological changes in AD [1]. Aβ is physiologically generated from the cleavage of amyloid precursor protein by β- and γ-secretases in the endoplasmic reticulum (ER) and trans-Golgi network or in the late endosome, then secreted into the extracellular space [2]. Therefore, various factors promoting the formation of Aβ oligomers may be involved in the key molecular mechanisms underlying the pathogenesis of AD. For instance, in many forms of early-onset familial AD (FAD), highly aggregative Aβ42 is over-produced by mutant Presenilin 1/2genes [3]. Furthermore, Aβ aggregation may be promoted by apolipoprotein E [4] and by environmental factors, such as oxidative stress and diabetes [5]. Oxidative stress-inducing metal ions, such as iron (Fe) [6], copper (Cu) [7], zinc (Zn) and aluminum (Al) may contribute to the formation of SPs/NFTs and neuronal damage in the AD brain. Al has long been under debate as to whether it is a risk factor for AD. Therefore, the purpose of our review was to provide research findings on the putative link between Al and AD to understand what has been resolved thus far and what should be investigated in the future.

History of Al and AD

In the 1930s, Al was shown to have an adjuvant action [8], and in the 1940s, intrathecal injection of Al was reported to cause epilepsy in monkeys [9-11]. Klatzo et al. [12] showed that injection of a vaccine with Holt's adjuvant containing Al phosphate into the brains of rabbits caused epilepsy, as well as neurofibrillary changes. Terry and Pena [13] reported that NFTs observed in AD brains resembled those of Al-induced neurofibrillary changes; however, they later reported a morphological difference between the two [14]. Nevertheless, these earliest reports suggested the involvement of Al in AD pathology.

By the 1970s, the association between Al and AD pathogenesis became a major topic of scientific discussion. Crapper and Dalton reported that administration of Al into cat brain induced memory impairment and neurofibrillary degeneration [15]. Increased levels of Al were documented in AD brain tissues [16-18]; however, these elevations were later found to be associated with aging and not with NFT levels [19]. Numerous studies have provided varying results (despite the use of similar methods) when measuring the levels of Al in human brain tissues, found to be both positive (Table 1) and negative (Table 2). Although the exact reason for these discrepancies is unclear, differences in the sample tissues may have been a factor. Indeed, since aging may increase Al levels in the brain [19], selection of age-matched control brain tissues may thus be important.

Al was also suggested to be the cause of dialysis-associated encephalopathy (DAE) [20,21]. However, the DAE pathology was found to be clearly different from AD pathology (for more information, see below). Thus, in the following years, the debate about association between Al and AD diminished.

Epidemiology of Al and AD

Contamination of drinking water with Al polychloride in Camelford, England (Camelford water pollution incident; 1988) occurred. It was later revealed that the prevalence of dementia was not increased [22]. While, it was reported that the prevalence of AD was 1.5-fold higher in the area with water containing Al over 0.11 mg/L compared with the area of water containing Al under 0.01 mg/L [23].

***Corresponding author:** Yasumasa Ohyagi, Department of Neurological Therapeutics, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan, Tel: +81-92-642-5340; Fax: +81-92-642-5352; E-mail: ohyagi@neuro.med.kyushu-u.ac.jp

Received March 04, 2013; **Accepted** July 05, 2013; **Published** July 10, 2013

Citation: Ohyagi Y, Miyoshi K (2013) Aluminum and Alzheimer's Disease: An Update. J Alzheimers Dis Parkinsonism 3: 118. doi:10.4172/2161-0460.1000118

Authors	Year	Reference	Methods	Number of subjects	
				AD	Control
Crapper et al.	1973	[16]	EAAS	5	3
Crapper et al.	1976	[17]	EAAS	10	7
Trapp et al.	1978	[97]	EAAS	4	4
Crapper et al.	1980	[18]	EAAS	18	17
Perl and Brody	1980	[98]	EDX	3	3
Traub et al.	1981	[99]	EAAS	7	26
Markesbery et al.	1981	[69]	NAA	12	28
Ward and Mason	1987	[100]	NAA	28	30
Lukiw et al.	1992	[101]	EAAS	21	17
Xu et al.	1992	[102]	EAAS	10	10
Corrigan et al.	1993	[103]	ICP-MS	12	12
Lovell et al.	1993	[104]	LMMS	7	5
Andrási et al.	1995	[105]	ICP-AES, INAA	9	20
Bouras et al.	1997	[106]	LMMS	4	3
Solomon et al.	2001	[107]	IF-CLM	5	5
Srivastava and Jain	2002	[108]	ICP-MS	4	4
Andrási et al.	2005	[109]	ICP-AES, INAA	3	3
Walton	2006	[110]	HS	6	6
Walton	2010	[111]	HS	5	5
Rushina et al.	2011	[112]	EAAS	29	27

EAAS: electrothermal atomic absorption spectrometry; EDX: energy-dispersive X-ray spectroscopy; NAA: neutron activation analysis; ICP-MS: inductively coupled plasma source mass spectrometry; LMMS: laser microprobe mass spectrometry; ICP-AES: inductively coupled plasma atomic emission spectrometry; INAA: instrumental neutron activation analysis; IF-CLM: immunofluorescence using confocal laser microscopy; HS: histological staining.

Table 1: Reports of increased levels of Aluminum (Al) in Alzheimer's disease (AD) brains.

Authors	Year	Reference	Methods	Number of subjects	
				AD	Control
McDermott et al.	1979	[19]	EAAS	10	9
Jacobs et al.	1989	[113]	EDX, EAAS	6	4
Dedman et al.	1992	[114]	EAAS	7	7
Edwardson et al.	1992	[115]	EAAS	8	8
Bjertness et al.	1996	[116]	EAAS	16	14
Makjanic et al.	1998	[117]	STIM	6	4
Akatsu et al.	2012	[118]	ICP-MS	18	16

EAAS: electrothermal atomic absorption spectrometry; EDX: energy-dispersive X-ray spectroscopy; STIM: scanning transmission ion microscopy; ICP- MS: inductively coupled plasma source mass spectrometry.

Table 2: Reports of the absence of increased levels of Al in AD brains.

Epidemiological research about the link between Al and dementia/AD continued in many other countries as follows.

A considerable number of epidemiological studies have been performed in industries associated with the manufacture of Al products, or in areas containing drinking water where Al was found. However, determining the occupational risk for AD has been difficult because of the limited size of sample numbers and difficulty of diagnosis [24]. Studies in the United Kingdom, Norway and Canada reported significant correlation between Al and AD [23-26] (Table 3). Neri and Hewitt [27] reported that Al concentration over 0.2 mg/L in water may increase the incident rate of AD (odds ratio =1.46) in Canada [27]. However, in another study from Canada, fluorine content, rather than Al, was found to be more correlated with the incident rate of AD [28], and the Canadian Study of Health and Aging (CSHA) suggested a low risk for AD from the consumption of water containing Al [29]. Such discrepancies in the same country may have resulted from differing regions in which the studies were conducted. While, Jacqmin-Gadda et al. [30] reported that Al content may be associated with cognitive dysfunction in the regions with low silicon content and low pH in water. More recently, a cohort study in France (Personnes agees Quid, PAQUID) reported that Al concentrations over 0.1 mg/L in water increased the risk for AD (relative risk=3.04), and high silica concentrations in water decreased the risk for AD [31]. However, obtaining highly reliable data from such epidemiological studies is considered to be quite difficult because although the human diet contains Al, absorption and levels of Al in blood are altered by various factors, such as silicon, pH, fluoride, Fe, calcium (Ca), carboxylic acids and renal function [32,33]. Some reports have suggested no significant correlation between Al and AD (Table 4). Bakar et al. [34] found no significant differences in the incidence of AD in areas with an acidic environment. Furthermore, many previous studies have revealed that consumption of tea or antacid drugs, which have high Al content, did not show a high incidence of AD [35-42]. These results indicate that various materials in drinking water and foods may act as the promoting or protecting factors for AD, and the effects of Al contained in water and foods may thus be masked by many factors.

Neurotoxicity of Al and Recommendation

Over the last 50 years, Al has been shown to be involved in epileptogenesis [9-11], and numerous *in vitro* and *in vivo* studies have reported on the neurotoxicity of Al. Al binds various organelles and proteins in the nucleus, cytoplasm, axon and synapse in neurons, exerting effects on the biological activity of magnesium, Fe, and Ca, thus interfering with the phosphorylation/dephosphorylation of nucleotides [43-45]. These actions may thus induce synaptic dysfunction [46-48], aberrant neuronal gene expression [49,50], over-stimulation of NMDA receptors leading to disruption of Ca homeostasis [51-53], oxidative stress [54], ER stress [55,56], mitochondrial damage [57,58] and others [59-62]. However, the major pathological hallmark of Al neurotoxicity was found to be the hyper-phosphorylation of neurofilament proteins [63-66]. Indeed, this characteristic was found in brain tissue of DAE, which has implicated Al as its cause [67,68]. Owing to the high binding affinity of Al with phosphate, Al may thus promote aggregation of

Authors	Year	Country	Reference	Number of subject	Age range
Martyn et al.	1989	UK	[23]	666 AD 519 other dementia	40-69 years
Flaten	1990	Norway	[25]	14,727 dementia	N/A
Frecker	1991	Canada	[26]	568,345 death 399 dementia	>70 years
Neri and Hewitt	1991	Canada	[27]	2,344 AD 2,232 controls	≥55 years
Forbes et al.	1991 1992 1994	Canada	[28] [119] [120]	782 people	45 years at baseline
Jacqmin et al. Jacqmin- Gadda et al.	1994 1996	France	[121] [30]	3,777 people	≥65 years
McLachlan et al.	1996	Canada	[122]	119 AD 51 controls	N/A
Gauthier et al.	2000	Canada	[123]	68 AD 68 controls	≥70 years
Rondeau et al.	2009	France	[31]	461 dementia incl. 364 AD	≥65 years

Table 3: Epidemiological reports showing a positive risk of Al-containing water for cognitive impairment, dementia, and AD.

Authors	Year	Country	Reference	Number of subject	Age range
Wettstein et al.	1991	Switzerland	[124]	805 people	81-85 years
				99 dementia	
Forster et al. Taylor et al.	1995	UK	[40] [125]	109 early-onset AD	<65 years
				109 controls	
Sohn et al.	1996	Korea	[126]	558 people	≥60 years
				45 dementia	
Martyn et al.	1997	UK	[127]	106 AD	42-75 years
				441 controls	
Molloy et al.	2007	Randomized case-control trial	[128]	16 AD	N/A
				17 controls	
				10 young volunteers	
Bakar et al.	2010	Turkey	[34]	273 people living in high Al area	N/A
				164 people in other area	

Table 4: Epidemiological and clinical trial reports showing an absence of a significant risk of Al-containing water for cognitive impairment, dementia, and AD.

Authors	Year	Reference	Methods	Number of subjects		Al detection
				AD	control	
Terry and Pena	1965	[13]	EDX	1	-	-
Perl and Brody	1980	[129]	EDX	3	3	+
Masters et al.	1985	[130]	EDX	6	-	+
Kobayashi et al.	1987	[131]	WDX	1	-	-
Jacobs et al.	1989	[113]	EDX	7	4	-
Moretz et al.	1990	[132]	EDX	3	-	-
Chafi et al.	1991	[133]	WDX, SIMS	7	-	-
Sparkman	1993	[134]	EDX	N/A	N/A	-
Lovell et al.	1993	[104]	LMMS	7	5	- (+ in neuron)
Kasa et al.	1995	[135]	solachrone azurine	10	5	±
Bouras et al.	1997	[106]	LMMS	4	3	+
Reusche	1997	[136]	LMMS	1 (DAE)	-	- (+ in DAE)
Makjanic et al.	1998	[117]	STIM	6	4	-
Murayama et al.	1999	[137]	Chelating autoclave	5	-	+

EDX: energy-dispersive X-ray spectroscopy; WDX: wavelength-dispersive X-ray microanalysis; SIMS: secondary ion mass spectrometry; LMMS: laser microprobe mass spectrometry; STIM: scanning transmission ion microscopy.

Table 5: Detection of Al in neurofibrillary tangles of AD brain tissues.

hyper-phosphorylated neurofilaments. However, evidence of such an effect may not directly indicate that Al plays a pivotal role in AD pathogenesis because NFTs in AD consists of p-tau.

Owing to the lack of consensus amongst epidemiological studies, it is still unclear whether oral Al intake increases the risk for AD. Therefore, this risk has not been approved by the European Food Safety Authority [32], Joint Food and Agriculture Organization of United Nations (FAO)/World Health Organization (WHO) [33], and Bundes institut für Risikobewertung. However, because aging is the major risk factor for sporadic AD, and that aging is a strong factor for promoting Al accumulation in brain tissue [19,69,70], the likelihood that Al is a risk factor for sporadic AD may thus be increased in the elderly. Impairment of the blood brain barrier or renal dysfunction during aging may promote the accumulation of Al in the brain. However, to study such effects may be quite difficult because aging itself is the strongest risk factor for AD, and some radical-generating metals other than Al, such as Fe, Cu and Zn may also facilitate Aβ oligomer formation and accelerate AD pathogenesis [71,72]. Although it is difficult to determine the safe doses of Al intake, the FAO/WHO presently recommend a tolerable weekly intake of 2 mg /kg body weight [33].

Does Al Associate with AD Pathology?

Whether Al is involved in the onset and progression AD remains an important issue. Many previous reports have suggested that various molecular mechanisms contribute to AD pathogenesis. To date, the widely accepted major factors are: Aβ (particularly Aβ oligomers) aggregation, phosphorylation/aggregation of tau protein (forming NFTs), oxidative stress, mitochondrial damage and synaptic dysfunction [73]. Therefore, the influence of Al on these pathological characteristics of AD has been explored. Studies have indicated that Almay be associated with the aggregation of Aβ [74,75] and p-tau [74-80], and may also be involved in Aβ deposition [81-84]. Al accumulation was shown to not consistently coincide with NFTs (Table 5) and SPs (Table 6). Furthermore, the concentration of Al in biological fluids is less than 1 μM (Bush AI, personal communication). Al accumulation was shown to not consistently coincide with NFTs (Table 5) and SPs (Table 6). Thus the role of Al in the formation of NFTs and SPs compared with other metal ions, such as Zn, Cu and Fe may not be as prominent. Zn is a key modulator for synaptic neural transmission, reaching 150-300 μM during synaptic activity, thus possibly contributing to Aβ aggregation [85]. Also, trace amounts of Cu were shown to induce Aβ accumulation in brain tissues of cholesterol-fed rabbits [86]. Therefore, the definitive involvement of Al in NFT/SP formation in the AD brain is difficult to elucidate. Nevertheless, Al itself may promote neuronal damage independently of NFT/SP.

As previously mentioned in this review, the Al hypothesis for AD was based on a pathological similarity of neurofibrillary degeneration seen in both the AD and DAE brain. However, Reusche et al. [87] found that in brain tissue from dialysis patients, only 1 case out of 50 exhibited the accumulation of Aβ42 and p-tau. Phosphorylated neurofilaments and cytoplasmic argyrophilic inclusions have been shown to be characteristics of Al-induced pathology in DAE rather than the paired helical filaments that are consistently observed in AD [67,68,87]. Remarkably, Al-containing lysosome-derived argyrophilic inclusion in neurons and glial cells is a characteristic of DAE in those brain tissues. Overall, pathological findings between AD and DAE are different.

Authors	Year	Reference	Methods	Number of subjects		Al detection
				AD	control	
Masters et al.	1985	[130]	EDX	6	-	+
Candy et al.	1986	[138]	EDX, SIMS	7	-	+
Jacobs et al.	1989	[113]	EDX	7	4	-
Larsson et al.	1990	[139]	Proton microprobe	2	-	-
Moretz et al.	1990	[132]	EDX	3	-	-
Senitz and Blüthner	1990	[140]	Morin staining	3	-	+
Chafi et al.	1991	[133]	WDX, SIMS	7	-	-
Landsberg et al.	1992	[141]	Proton (nuclear) microscopy	5	2	-
Landsberg et al.	1993	[142]	Proton (nuclear) microscopy	6	2	±
Kasa et al.	1995	[135]	solachrone azurine	10	5	±
Yumoto et al.	2009	[143]	TEM-EDX	5	-	+

EDX: energy-dispersive X-ray spectroscopy; WDX: wavelength-dispersive X-ray microanalysis; SIMS: secondary ion mass spectrometry; TEM-EDX: energy-dispersive X-ray spectroscopy combined with transmission electron microscopy.

Table 6: Detection of Al in senile plaques of AD brain tissues.

Does Al Promote Dementia in AD Models?

Numerous studies of transgenic (Tg) animal models of AD have been performed to further confirm the possibility that Al is not directly linked to AD, but may enhance cognitive dysfunction and/or AD pathology. Pratico et al. [88] fed Tg2576 mice an Al-enriched diet (2 mg/kg/day, from 3-12 months old), finding that levels of isoprostane and Aβ increased and Aβ deposition was enhanced (compared with wild-type [wt]). Furthermore, vitamin E, an anti-oxidant, reversed such responses, which may support the idea that Al accelerates oxidative stress and AD pathology. Ribes et al. [89] fed Tg2576 or wt mice with a low dose of Al lactate (1 mg/g, from 5 months for 120 days), and found impaired cognition via oxidative stress in wt, which may not have interacted with the amyloidogenic pathway. Tg2576 mice fed the same diet (5-11 months old) showed that Al may act as a pro-oxidant agent in both Tg2576 and wild-type mice [90]. Al levels have also been shown to be higher in the hippocampus than in the cerebellum and cortex in both Tg2576 and wt mice [91]. Altogether, these studies have revealed that long-term exposure on a diet containing Al may induce oxidative stress and cognitive impairment with or without an exacerbated AD pathology. Recently, Akiyama et al. [92] found that administering Al or Zn in drinking water (100 mg/kg/day, from 8 months for 4-10 months) to Tg2576 or Tg2576/tau-P301L mice did not enhance the deposition of Aβ or tau deposition, nor the increase insoluble Aβ or Aβ oligomers. Although cognitive function and oxidative stress markers were not analyzed in the study, it is evident that an intake of such a high dose of Al did not enhance AD pathology related to the mutation of amyloid precursor protein. Overall, it is unclear as to why these studies have shown contradictory results. Our re-evaluation of these previous studies of animal experiments based on the differing types of Al salts used did not account for the discrepancies.

Furthermore, the Tg2576 model is an early-onset FAD model. Therefore, the effects of Al intake on AD pathology and cognitive function remain to be observed in a model of the late-onset sporadic AD. Unfortunately, such animal models are currently not available. Interestingly, however, chronic intake of low dose Al in aged wt rats was shown to cause cognitive deterioration and neuronal loss in regions usually affected by AD, the entorhinal cortex and hippocampus [93].

Therefore, Al intake may not be a strong factor for the cause or promotion of early-onset FAD pathogenesis. Nevertheless, long-term intake of low dose Al may promote oxidative stress and neuronal damage, thus contributing to the cognitive decline in the elderly population irrespective of their risk for developing this disease. Such a possible effect may not be specific for Al, and other radical-generating metals may also contribute to the cognitive decline.

How Can We Understand the Real Role of Al?

There are a number of environmental factors (e.g. aging, ischemia, diabetes, trauma, smoking) that pose risks for AD and cognitive decline [94]. As reviewed here, Al may not be the major environmental risk factor for the onset and progression of AD. However, Al might contribute to the acceleration of cognitive decline, as well as other free radical-generating metals, in the elderly population irrespective of whether they have AD. To better understand this hypothesis, a large cohort study, rather than an epidemiological investigation, may be necessary, for example the worldwide AD Neuroimaging Initiative (ADNI) [95]. Because brain Aβ accumulation may start 10-20 years before the onset of mild cognitive impairment or the prodromal AD stages [96], it may thus be necessary to evaluate the involvement of free radical-generating metal ions (Fe, Cu, Zn and Al) during these stages. Furthermore, levels of these metals in the cerebrospinal fluid (CSF) should be measured, followed by correlation analysis with amyloid imaging, AD biomarkers in the CSF, and cognitive examination outcomes.

Conclusion

Previous epidemiological, biochemical, and pathological studies have provided quite conflicting results regarding the involvement of Al in AD pathogenesis. Findings from studies involving DAE and AD mouse models therefore suggest that Al intake is not a direct cause for AD. However, Al and other free-radical generating metals show neurotoxic activity *in vitro*, thus indicating that they may promote cognitive impairment in rodents and humans because these metals accumulate in the aging brain. Therefore, above normal intake of Al (and other metals) is an environmental factor that may promote cognitive decline in the aged population, irrespective of whether they are at risk for developing AD. More advanced cohort studies are thus necessary to understand the absolute risk of Al (and other metals) for AD.

References

1. Larson ME, Lesné SE (2012) Soluble Aß oligomer production and toxicity. J Neurochem 120: 125-139.
2. Xia W (2001) Amyloid metabolism and secretases in Alzheimer's disease. Curr Neurol Neurosci Rep 1: 422-427.
3. Newman M, Musgrave IF, Lardelli M (2007) Alzheimer disease: amyloidogenesis, the presenilins and animal models. Biochim Biophys Acta 1772: 285-297.
4. Kim J, Basak JM, Holtzman DM (2009) The role of apolipoprotein E in Alzheimer's disease. Neuron 63: 287-303.
5. Zhao WQ, Townsend M (2009) Insulin resistance and amyloidogenesis as common molecular foundation for type 2 diabetes and Alzheimer's disease. Biochim Biophys Acta 1792: 482-496.
6. Castellani RJ, Moreira PI, Perry G, Zhu X (2012) The role of iron as a mediator of oxidative stress in Alzheimer disease. Biofactors 38: 133-138.
7. Eskici G, Axelsen PH (2012) Copper and oxidative stress in the pathogenesis of Alzheimer's disease. Biochemistry 51: 6289-6311.
8. Marrack P, McKee AS, Munks MW (2009) Towards an understanding of the adjuvant action of aluminium. Nat Rev Immunol 9: 287-293.
9. Kopeloff LM, Barrera SE, Kopeloff N (1942) Recurrent convulsive seizures in animals produced by immunologic and chemical means. Am J Psychiatry 98: 881-902.
10. Chusid JG, Pacella BL, Kopeloff LM, Kopeloff N (1951) Chronic epilepsy in the monkey following multiple intracerebral injection of alumina cream. Proc Soc Exp Biol Med 78: 53-54.
11. Chusid JG, Kopeloff LM, Kopeloff N (1956) Epileptic effects of intracisternal alumina cream in monkeys. J Neurosurg 13: 582-586.
12. Klatzo I, Wisniewski H, Streicher E (1965) Experimental Production Of Neurofibrillary Degeneration. I. Light Microscopic Observations. J Neuropathol Exp Neurol 24: 187-199.
13. Terry RD, Pena C (1965) Experimental Production Of Neurofibrillary Degeneration 2. Electron Microscopy, Phosphatase Histochemistry And Electron Probe Analysis. J Neuropathol Exp Neurol 24: 200-210.
14. Wisniewski H, Terry RD, Hirano A (1970) Neurofibrillary pathology. J Neuropathol Exp Neurol 29: 163-176.
15. Crapper DR, Dalton AJ (1973) Alterations in short-term retention, conditioned avoidance response acquisition and motivation following aluminum induced neurofibrillary degeneration. Physiol Behav 10: 925-933.
16. Crapper DR, Krishnan SS, Dalton AJ (1973) Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration. Science 180: 511-513.
17. Crapper DR, Krishnan SS, Quittkat S (1976) Aluminium, neurofibrillary degeneration and Alzheimer's disease. Brain 99: 67-80.

18. Crapper DR, Quittkat S, Krishnan SS, Dalton AJ, De Boni U (1980) Intranuclear aluminum content in Alzheimer's disease, dialysis encephalopathy, and experimental aluminum encephalopathy. Acta Neuropathol 50: 19-24.

19. McDermott JR, Smith AI, Iqbal K, Wisniewski HM (1979) Brain aluminum in aging and Alzheimer disease. Neurology 29: 809-814.

20. Alfrey AC, LeGendre GR, Kaehny WD (1976) The dialysis encephalopathy syndrome. Possible aluminum intoxication. N Engl J Med 294: 184-188.

21. Flendrig JA, Kruis H, Das HA (1976) Letter: Aluminum and dialysis dementia. Lancet 1(7971): 1235.

22. David AS, Wessely SC (1995) The legend of Camelford: medical consequences of a water pollution accident. J Psychosom Res 39: 1-9.

23. Martyn CN, Barker DJ, Osmond C, Harris EC, Edwardson JA, et al. (1989) Geographical relation between Alzheimer's disease and aluminum in drinking water. Lancet 1(8629): 59-62.

24. Santibáñez M, Bolumar F, García AM (2007) Occupational risk factors in Alzheimer's disease: a review assessing the quality of published epidemiological studies. Occup Environ Med 64: 723-732.

25. Flaten TP (1990) Geographical associations between aluminium in drinking water and death rates with dementia (including Alzheimer's disease), Parkinson's disease and amyotrophic lateral sclerosis in Norway. Environ Geochem Health 12: 152-167.

26. Frecker MF (1991) Dementia in Newfoundland: identification of a geographical isolate? J Epidemiol Community Health 45: 307-311.

27. Neri LC, Hewitt D (1991) Aluminium, Alzheimer's disease, and drinking water. Lancet 338: 390.

28. Forbes WF, Hayward LM, Agwani N (1991) Dementia, aluminium, and fluoride. Lancet 338: 1592-1593.

29. The Canadian Study of Health and Aging (1994) Risk factors for Alzheimer's disease in Canada. Neurology 44: 2073-2080.

30. Jacqmin-Gadda H, Commenges D, Letenneur L, Dartigues JF (1996) Silica and aluminum in drinking water and cognitive impairment in the elderly. Epidemiology 7: 281-285.

31. Rondeau V, Jacqmin-Gadda H, Commenges D, Helmer C, Dartigues JF (2009) Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. Am J Epidemiol 169: 489-496.

32. European Food Safety Authority (EFSA) (2008) Safety of aluminium from dietary intake. EFSA J 754: 1-34. (http://www.efsa.europa.eu/en/efsajournal/doc/754.pdf)

33. The seventy-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (2012) Safety evaluation of certain food additives and contaminants. WHO FOOD ADDITIVES SERIES 65: 4-81.

34. Bakar C, Karaman HI, Baba A, Sengünalp F (2010) Effect of high aluminum concentration in water resources on human health, case study: Biga Peninsula, northwest part of Turkey. Arch Environ Contam Toxicol 58: 935-944.

35. Heyman A, Wilkinson WE, Stafford JA, Helms MJ, Sigmon AH, et al. (1984) Alzheimer's disease: a study of epidemiological aspects. Ann Neurol 15: 335-341.

36. Amaducci LA, Fratiglioni L, Rocca WA, Fieschi C, Livrea P, et al. (1986) Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of an Italian population. Neurology 36: 922-931.

37. Colin-Jones D, Langman MJ, Lawson DH, Vessey MP (1989) Alzheimer's disease in antacid users. Lancet 1: 1453.

38. Broe GA, Henderson AS, Creasey H, McCusker E, Korten AE, et al. (1990) A case-control study of Alzheimer's disease in Australia. Neurology 40: 1698-1707.

39. Graves AB, White E, Koepsell TD, Reifler BV, van Belle G, et al. (1990) The association between aluminum-containing products and Alzheimer's disease. J Clin Epidemiol 43: 35-44.

40. Forster DP, Newens AJ, Kay DW, Edwardson JA (1995) Risk factors in clinically diagnosed presenile dementia of the Alzheimer type: a case-control study in northern England. J Epidemiol Community Health 49: 253-258.

41. Lindsay J, Laurin D, Verreault R, Hébert R, Helliwell B, et al. (2002) Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol 156: 445-453.

42. Yokel RA, Florence RL (2008) Aluminum bioavailability from tea infusion. Food Chem Toxicol 46: 3659-3663.

43. McLachlan DR, Kruck TP, Lukiw WJ, Krishnan SS (1991) Would decreased aluminum ingestion reduce the incidence of Alzheimer's disease? CMAJ 145: 793-804.

44. Tomljenovic L (2011) Aluminum and Alzheimer's disease: after a century of controversy, is there a plausible link? J Alzheimers Dis 23: 567-598.

45. Kawahara M, Kato-Negishi M (2011) Link between Aluminum and the Pathogenesis of Alzheimer's Disease: The Integration of the Aluminum and Amyloid Cascade Hypotheses. Int J Alzheimers Dis 2011: 276393.

46. Meiri H, Banin E, Roll M, Rousseau A (1993) Toxic effects of aluminium on nerve cells and synaptic transmission. Prog Neurobiol 40: 89-121.

47. Canales JJ, Corbalán R, Montoliu C, Llansola M, Monfort P, et al. (2001) Aluminium impairs the glutamate-nitric oxide-cGMP pathway in cultured neurons and in rat brain in vivo: molecular mechanisms and implications for neuropathology. J Inorg Biochem 87: 63-69.

48. Colomina MT, Roig JL, Sánchez DJ, Domingo JL (2002) Influence of age on aluminum-induced neurobehavioral effects and morphological changes in rat brain. Neurotoxicology 23: 775-781.

49. Alexandrov PN, Zhao Y, Pogue AI, Tarr MA, Kruck TP, et al. (2005) Synergistic effects of iron and aluminum on stress-related gene expression in primary human neural cells. J Alzheimers Dis 8: 117-127.

50. Gatta V, Drago D, Fincati K, Valenti MT, Dalle Carbonare L, et al. (2011) Microarray analysis on human neuroblastoma cells exposed to aluminum, ß(1-42)-amyloid or the ß(1-42)-amyloid aluminum complex. PLoS One 6: e15965.

51. Exley C (1999) A molecular mechanism of aluminium-induced Alzheimer's disease? J Inorg Biochem 76: 133-140.

52. Nday CM, Drever BD, Salifoglou T, Platt B (2010) Aluminium interferes with hippocampal calcium signaling in a species-specific manner. J Inorg Biochem 104: 919-927.

53. Walton JR (2012) Aluminum disruption of calcium homeostasis and signal transduction resembles change that occurs in aging and Alzheimer's disease. J Alzheimers Dis 29: 255-273.

54. Exley C (2004) The pro-oxidant activity of aluminum. Free Radic Biol Med 36: 380-387.

55. Ghribi O, Herman MM, Savory J (2002) The endoplasmic reticulum is the main site for caspase-3 activation following aluminum-induced neurotoxicity in rabbit hippocampus. Neurosci Lett 324: 217-221.

56. Rodella LF, Ricci F, Borsani E, Stacchiotti A, Foglio E, et al. (2008) Aluminium exposure induces Alzheimer's disease-like histopathological alterations in mouse brain. Histol Histopathol 23: 433-439.

57. Savory J, Herman MM, Ghribi O (2003) Intracellular mechanisms underlying aluminum-induced apoptosis in rabbit brain. J Inorg Biochem 97: 151-154.

58. Niu PY, Niu Q, Zhang QL, Wang LP, He SE, et al. (2005) Aluminum impairs rat neural cell mitochondria in vitro. Int J Immunopathol Pharmacol 18: 683-689.

59. Julka D, Gill KD (1996) Altered calcium homeostasis: a possible mechanisms of aluminium-induced neurotoxicity. Biochim Biophys Acta 1315: 47-54.

60. Levi R, Wolf T, Fleminger G, Solomon B (1998) Immuno-detection of aluminium and aluminium induced conformational changes in calmodulin--implications in Alzheimer's disease. Mol Cell Biochem 189: 41-46.

61. Brenner S (2002) Aluminum neurotoxicity is reduced by dantrolene and dimethyl sulfoxide in cultured rat hippocampal neurons. Biol Trace Elem Res 86: 85-89.

62. Kumar V, Gill KD (2009) Aluminium neurotoxicity: neurobehavioural and oxidative aspects. Arch Toxicol 83: 965-978.

63. Shea TB, Beermann ML, Wang FS (1995) Relative susceptibility of cytoskeleton-associated and soluble neurofilament subunits to aluminum exposure in intact cells. A possible mechanism for reduction of neurofilament axonal transport during aluminum neurotoxicity. Mol Chem Neuropathol 24: 203-219.

64. Gaytan-Garcia S, Kim H, Strong MJ (1996) Spinal motor neuron neuroaxonal spheroids in chronic aluminum neurotoxicity contain phosphatase-resistant high molecular weight neurofilament (NFH). Toxicology 108: 17-24.

65. van der Voet GB, Schijns O, de Wolff FA (1999) Fluoride enhances the effect of aluminium chloride on interconnections between aggregates of hippocampal neurons. Arch Physiol Biochem 107: 15-21.

66. Kushkuley J, Metkar S, Chan WK, Lee S, Shea TB (2010) Aluminum induces neurofilament aggregation by stabilizing cross-bridging of phosphorylated c-terminal sidearms. Brain Res 1322: 118-123.

67. Scholtz CL, Swash M, Gray A, Kogeorgos J, Marsh F (1987) Neurofibrillary neuronal degeneration in dialysis dementia: a feature of aluminum toxicity. Clin Neuropathol 6: 93-97.

68. Shirabe T, Irie K, Uchida M (2002) Autopsy case of aluminum encephalopathy. Neuropathology 22: 206-210.

69. Markesbery WR, Ehmann WD, Hossain TI, Alauddin M, Goodin DT (1981) Instrumental neutron activation analysis of brain aluminum in Alzheimer disease and aging. Ann Neurol 10: 511-516.

70. Ganrot PO (1986) Metabolism and possible health effects of aluminum. Environ Health Perspect 65: 363-441.

71. Bonda DJ, Lee HG, Blair JA, Zhu X, Perry G, et al. (2011) Role of metal dyshomeostasis in Alzheimer's disease. Metallomics 3: 267-270.

72. Curtain CC, Ali F, Volitakis I, Cherny RA, Norton RS, et al. (2001) Alzheimer's disease amyloid-beta binds copper and zinc to generate an allosterically ordered membrane-penetrating structure containing superoxide dismutase-like subunits. J Biol Chem 276: 20466-20473.

73. Reddy PH (2011) Abnormal tau, mitochondrial dysfunction, impaired axonal transport of mitochondria, and synaptic deprivation in Alzheimer's disease. Brain Res 1415: 136-148.

74. Exley C (2006) Aluminium and iron, but neither copper nor zinc, are key to the precipitation of beta-sheets of Abeta_{42} in senile plaque cores in Alzheimer's disease. J Alzheimers Dis 10: 173-177.

75. Drago D, Bolognin S, Zatta P (2008) Role of metal ions in the abeta oligomerization in Alzheimer's disease and in other neurological disorders. Curr Alzheimer Res 5: 500-507.

76. Shin RW, Lee VM, Trojanowski JQ (1994) Aluminum modifies the properties of Alzheimer's disease PHF tau proteins in vivo and in vitro. J Neurosci 14: 7221-7233.

77. Shin RW, Kruck TP, Murayama H, Kitamoto T (2003) A novel trivalent cation chelator Feralex dissociates binding of aluminum and iron associated with hyperphosphorylated tau of Alzheimer's disease. Brain Res 961: 139-146.

78. Yamamoto H, Saitoh Y, Yasugawa S, Miyamoto E (1990) Dephosphorylation of tau factor by protein phosphatase 2A in synaptosomal cytosol fractions, and inhibition by aluminum. J Neurochem 55: 683-690.

79. Muma NA, Singer SM (1996) Aluminum-induced neuropathology: transient changes in microtubule-associated proteins. Neurotoxicol Teratol 18: 679-690.

80. Savory J, Huang Y, Herman MM, Reyes MR, Wills MR (1995) Tau immunoreactivity associated with aluminum maltolate-induced neurofibrillary degeneration in rabbits. Brain Res 669: 325-329.

81. Nitsch RM, Slack BE, Wurtman RJ, Growdon JH (1992) Release of Alzheimer amyloid precursor derivatives stimulated by activation of muscarinic acetylcholine receptors. Science 258: 304-307.

82. Xu H, Greengard P, Gandy S (1995) Regulated formation of Golgi secretory vesicles containing Alzheimer beta-amyloid precursor protein. J Biol Chem 270: 23243-23245.

83. Sakamoto T, Saito H, Ishii K, Takahashi H, Tanabe S, et al. (2006) Aluminum inhibits proteolytic degradation of amyloid beta peptide by cathepsin D: a potential link between aluminum accumulation and neuritic plaque deposition. FEBS Lett 580: 6543-6549.

84. Luo Y, Niu F, Sun Z, Cao W, Zhang X, et al. (2009) Altered expression of Abeta metabolism-associated molecules from D-galactose/AlCl(3) induced mouse brain. Mech Ageing Dev 130: 248-252.

85. Sensi SL, Paoletti P, Koh JY, Aizenman E, Bush AI, et al. (2011) The neurophysiology and pathology of brain zinc. J Neurosci 31: 16076-16085.

86. Sparks DL, Schreurs BG (2003) Trace amounts of copper in water induce beta-amyloid plaques and learning deficits in a rabbit model of Alzheimer's disease. Proc Natl Acad Sci U S A 100: 11065-11069.

87. Reusche E, Koch V, Lindner B, Harrison AP, Friedrich HJ (2001) Alzheimer morphology is not increased in dialysis-associated encephalopathy and long-term hemodialysis. Acta Neuropathol 101: 211-216.

88. Praticò D, Uryu K, Sung S, Tang S, Trojanowski JQ, et al. (2002) Aluminum modulates brain amyloidosis through oxidative stress in APP transgenic mice. FASEB J 16: 1138-1140.

89. Ribes D, Colomina MT, Vicens P, Domingo JL (2008) Effects of oral aluminum exposure on behavior and neurogenesis in a transgenic mouse model of Alzheimer's disease. Exp Neurol 214: 293-300.

90. Garcia T, Esparza JL, Nogués MR, Romeu M, Domingo JL, et al. (2010) Oxidative stress status and RNA expression in hippocampus of an animal model of Alzheimer's disease after chronic exposure to aluminum. Hippocampus 20: 218-225.

91. Esparza JL, Garcia T, Gómez M, Nogués MR, Giralt M, et al. (2011) Role of deferoxamine on enzymatic stress markers in an animal model of Alzheimer's disease after chronic aluminum exposure. Biol Trace Elem Res 141: 232-245.

92. Akiyama H, Hosokawa M, Kametani F, Kondo H, Chiba M, et al. (2012) Long-term oral intake of aluminum or zinc does not accelerate Alzheimer pathology in AβPP and AβPP/tau transgenic mice. Neuropathology 32: 390-397.

93. Walton JR (2012) Cognitive deterioration and associated pathology induced by chronic low-level aluminum ingestion in a translational rat model provides an explanation of Alzheimer's disease, tests for susceptibility and avenues for treatment. Int J Alzheimers Dis 2012: 914947.

94. Mayeux R, Stern Y (2012) Epidemiology of Alzheimer disease. Cold Spring Harb Perspect Med 2.

95. Carrillo MC, Bain LJ, Frisoni GB, Weiner MW (2012) Worldwide Alzheimer's disease neuroimaging initiative. Alzheimers Dement 8: 337-342.

96. Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, et al. (2012) The Alzheimer's Disease Neuroimaging Initiative: a review of papers published since its inception. Alzheimers Dement 8: S1-68.

97. Trapp GA, Miner GD, Zimmerman RL, Mastri AR, Heston LL (1978) Aluminum levels in brain in Alzheimer's disease. Biol Psychiatry 13: 709-718.

98. Perl DP, Brody AR (1980) Alzheimer's disease: X-ray spectrometric evidence of aluminum accumulation in neurofibrillary tangle-bearing neurons. Science 208: 297-299.

99. Traub RD, Rains TC, Garruto RM, Gajdusek DC, Gibbs CJ Jr (1981) Brain destruction alone does not elevate brain aluminum. Neurology 31: 986-990.

100. Ward NI, Mason JA (1987) Neutron activation analysis techniques for identifying elemental status in Alzheimer's disease. J Radioanal Nucl Chem 113: 515-526.

101. Lukiw WJ, Krishnan B, Wong L, Kruck TP, Bergeron C, et al. (1992) Nuclear compartmentalization of aluminum in Alzheimer's disease (AD). Neurobiol Aging 13: 115-121.

102. Xu N, Majidi V, Markesbery WR, Ehmann WD (1992) Brain aluminum in Alzheimer's disease using an improved GFAAS method. Neurotoxicology 13: 735-743.

103. Corrigan FM, Reynolds GP, Ward NI (1993) Hippocampal tin, aluminum and zinc in Alzheimer's disease. Biometals 6: 149-154.

104. Lovell MA, Ehmann WD, Markesbery WR (1993) Laser microprobe analysis of brain aluminum in Alzheimer's disease. Ann Neurol 33: 36-42.

105. Andrási E, Farkas E, Scheibler H, Réffy A, Bezúr L (1995) Al, Zn, Cu, Mn and Fe levels in brain in Alzheimer's disease. Arch Gerontol Geriatr 21: 89-97.

106. Bouras C, Giannakopoulos P, Good PF, Hsu A, Hof PR, et al. (1997) A laser microprobe mass analysis of brain aluminum and iron in dementia pugilistica: comparison with Alzheimer's disease. Eur Neurol 38: 53-58.

107. Solomon B, Koppel R, Jossiphov J (2001) Immunostaining of calmodulin and aluminium in Alzheimer's disease-affected brains. Brain Res Bull 55: 253-256.

108. Srivastava RA, Jain JC (2002) Scavenger receptor class B type I expression and elemental analysis in cerebellum and parietal cortex regions of the Alzheimer's disease brain. J Neurol Sci 196: 45-52.

109. Andrási E, Páli N, Molnár Z, Kösel S (2005) Brain aluminum, magnesium and phosphorus contents of control and Alzheimer-diseased patients. J Alzheimers Dis 7: 273-284.

110. Walton JR (2006) Aluminum in hippocampal neurons from humans with Alzheimer's disease. Neurotoxicology 27: 385-394.

111. Walton JR (2010) Evidence for participation of aluminum in neurofibrillary tangle formation and growth in Alzheimer's disease. J Alzheimers Dis 22: 65-72.

112. Rusina R, Matej R, Kasparova L, Kukal J, Urban P (2011) Higher aluminum concentration in Alzheimer's disease after Box-Cox data transformation. Neurotox Res 20: 329-333.

113. Jacobs RW, Duong T, Jones RE, Trapp GA, Scheibel AB (1989) A reexamination of aluminum in Alzheimer's disease: analysis by energy dispersive X-ray microprobe and flameless atomic absorption spectrophotometry. Can J Neurol Sci 16: 498-503.

114. Dedman DJ, Treffry A, Candy JM, Taylor GA, Morris CM, et al. (1992) Iron and aluminium in relation to brain ferritin in normal individuals and Alzheimer's-disease and chronic renal-dialysis patients. Biochem J 287 : 509-514.

115. Edwardson JA, Candy JM, Ince PG, McArthur FK, Morris CM, et al. (1992) Aluminium accumulation, beta-amyloid deposition and neurofibrillary changes in the central nervous system. Ciba Found Symp 169: 165-179.

116. Bjertness E, Candy JM, Torvik A, Ince P, McArthur F, et al. (1996) Content of brain aluminum is not elevated in Alzheimer disease. Alzheimer Dis Assoc Disord 10: 171-174.

117. Makjanic J, McDonald B, Li-Hsian Chen CP, Watt F (1998) Absence of aluminium in neurofibrillary tangles in Alzheimer's disease. Neurosci Lett 240: 123-126.

118. Akatsu H, Hori A, Yamamoto T, Yoshida M, Mimuro M, et al. (2012) Transition metal abnormalities in progressive dementias. Biometals 25: 337-350.

119. Forbes WF, Hayward LM, Agwani N (1992) Geochemical risk factors for mental functioning, based on the Ontario Longitudial Study of Aging (LAS). I. Results from a preliminary investigation. Can J Aging 11: 269-280.

120. Forbes WF, McAiney CA, Hayward LM, Agwani N (1994) Geochemical risk factors for mental functioning, based on the Ontario longitudinal study of aging (LSA): II. The role of pH. Can J Aging 13: 249-267.

121. Jacqmin H, Commenges D, Letenneur L, Barberger-Gateau P, Dartigues JF (1994) Components of drinking water and risk of cognitive impairment in the elderly. Am J Epidemiol 139: 48-57.

122. McLachlan DR, Bergeron C, Smith JE, Boomer D, Rifat SL (1996) Risk for neuropathologically confirmed Alzheimer's disease and residual aluminum in municipal drinking water employing weighted residential histories. Neurology 46: 401-405.

123. Gauthier E, Fortier I, Courchesne F, Pepin P, Mortimer J, et al. (2000) Aluminum forms in drinking water and risk of Alzheimer's disease. Environ Res 84: 234-246.

124. Wettstein A, Aeppli J, Gautschi K, Peters M (1991) Failure to find a relationship between mnestic skills of octogenarians and aluminum in drinking water. Int Arch Occup Environ Health 63: 97-103.

125. Taylor GA, Newens AJ, Edwardson JA, Kay DW, Forster DP (1995) Alzheimer's disease and the relationship between silicon and aluminium in water supplies in northern England. J Epidemiol Community Health 49: 323-324.

126. Sohn S-J, Shin J-H, Park Y-S, Rhee J-A, Choi J-S(1996) Components of drinking water and risk of cognitive impairment in the rural elderly. Chonnam J Med Sci 9: 189-193.

127. Martyn CN, Coggon DN, Inskip H, Lacey RF, Young WF (1997) Aluminum concentrations in drinking water and risk of Alzheimer's disease. Epidemiology 8: 281-286.

128. Molloy DW, Standish TI, Nieboer E, Turnbull JD, Smith SD, et al. (2007) Effects of acute exposure to aluminum on cognition in humans. J Toxicol Environ Health A 70: 2011-2019.

129. Perl DP, Brody AR (1980) Alzheimer's disease: X-ray spectrometric evidence of aluminum accumulation in neurofibrillary tangle-bearing neurons. Science 208: 297-299.

130. Masters CL, Multhaup G, Simms G, Pottgiesser J, Martins RN, et al. (1985) Neuronal origin of a cerebral amyloid: neurofibrillary tangles of Alzheimer's disease contain the same protein as the amyloid of plaque cores and blood vessels. EMBO J 4: 2757-2763.

131. Kobayashi S, Hirota N, Saito K, Utsuyama M (1987) Aluminum accumulation in tangle-bearing neurons of Alzheimer's disease with Balint's syndrome in a long-term aluminum refiner. Acta Neuropathol 74: 47-52.

132. Moretz RC, Iqbal K, Wisniewski HM (1990) Microanalysis of Alzheimer disease NFT and plaques. Environ Geochem Health 12: 15-16.

133. Chafi AH, Hauw JJ, Rancurel G, Berry JP, Galle C (1991) Absence of aluminium in Alzheimer's disease brain tissue: electron microprobe and ion microprobe studies. Neurosci Lett 123: 61-64.

134. Sparkman DR (1993) X-ray probe microanalysis of Alzheimer disease soluble and insoluble paired helical filaments. Neurosci Lett 151: 153-157.

135. Kasa P, Szerdahelyi P, Wisniewski HM (1995) Lack of topographical relationship between sites of aluminum deposition and senile plaques in the Alzheimer's disease brain. Acta Neuropathol 90: 526-531.

136. Reusche E (1997) Argyrophilic inclusions distinct from Alzheimer neurofibrillary changes in one case of dialysis-associated encephalopathy. Acta Neuropathol 94: 612-616.

137. Murayama H, Shin RW, Higuchi J, Shibuya S, Muramoto T, et al. (1999) Interaction of aluminum with PHFtau in Alzheimer's disease neurofibrillary degeneration evidenced by desferrioxamine-assisted chelating autoclave method. Am J Pathol 155: 877-885.

138. Candy JM, Oakley AE, Klinowski J, Carpenter TA, Perry RH, et al. (1986) Aluminosilicates and senile plaque formation in Alzheimer's disease. Lancet 1: 354-357.

139. Larsson NP-O, Tapper UAS, Sturesson K, Odselius R, Brun A(1990) Technical aspects of nuclear microprobe analysis of senile plaques from Alzheimer patients. Nuc Inst Meth Phys Res B 49:472-475.

140. Senitz D, Blüthner K (1990) The presence of aluminum in cerebral vessels in Alzheimer's disease. Zentralbl Allg Pathol 136: 329-335.

141. Landsberg JP, McDonald B, Watt F (1992) Absence of aluminium in neuritic plaque cores in Alzheimer's disease. Nature 360: 65-68.

142. Landsberg J, McDonald B, Grime G, Watt F (1993) Microanalysis of senile plaques using nuclear microscopy. J Geriatr Psychiatry Neurol 6: 97-104.

143. Yumoto S, Kakimi S, Ohsaki A, Ishikawa A (2009) Demonstration of aluminum in amyloid fibers in the cores of senile plaques in the brains of patients with Alzheimer's disease. J Inorg Biochem 103: 1579-1584.