A review of epidemiologic studies on aluminum and silica in relation to Alzheimer's disease and associated disorders.

Virginie Rondeau

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Virginie Rondeau

INSERM U330, 146 rue Léo Saignat, 33076 Bordeaux

Email: ***Virginie.Rondeau@isped.u-bordeaux2.fr***

Abstract

Although the neurotoxicty of aluminium is now established, the association between aluminium and dementia or associated disorders is still debated. In this article a review of the different epidemiological articles published on this subject is presented. Different sources of exposure are considered (occupational exposure, aluminium-containing products ...) with an emphasis on drinking water. We have separated the different health effects of aluminium into three categories: neurological disorders (other than cognitive decline or AD), cognitive decline and dementia or Alzheimer's disease. Furthermore, we present the results obtained on silica in drinking water, another chemical constituent which could interact with aluminium.

Keywords: Neurological disorders - dementia - Aluminium - Silica.

1 Introduction

Alzheimer's disease (AD), the most common cause of senile dementia, is a progressive brain disorder which affects memory and other cognitive functions. Alzheimer's disease is characterized by a number of important pathological changes. There occurs a loss of neurons and synapses in many areas of the central nervous system. Abnormalities in the processing of the amyloid precursor protein are believed to be central to the pathogenesis of AD, initiating a pathological “cascade'” leading to the development of senile plaques and neurofibrillary tangles, cell death and dementia.

Although much effort has been devoted to identifying the genetic determinants of Alzheimer's disease /1/, it is likely that certain environmental factors play a role in this disease. Because of its proven neurotoxicity, aluminium (Al) may be one such factor. The hypothesis of a link between aluminium and AD has been supported by several biological findings /2,3,4,5/, but uncertainty still prevails. The involvement of Al as a risk factor for AD is suggested by the fact that it is found in several sources. Aluminium has been found in senile plaques and neurofibrillary tangles, as it has been reported by several studies /6/. However these results have been refuted /7/, and the presence of Al has been attributed to contamination of tissue samples by Al present in fixatives and staining reagents.

Dialysis encephalopathy /8/, a fatal brain disorder occurring in some patients with chronic renal failure, is one of the main observations in favor of the neurotoxicity of aluminium, because it proves that aluminium is able to reach the brain and to induce neurofibrillary degeneration and neuronal death. Furthermore, it is known from ^{26}Al tracer studies and from observations in humans and experimental animals that Al can enter the central nervous system.

There are now more and more studies showing that the relationship between aluminium in drinking water and the risk of AD or cognitive impairment must be examined after adjustment for other water constituents, which could play a confounding role by affecting the neurotoxicity of aluminium. In particular, the effect of silicon in tap water has been studied. Birchall et al /9/ showed that silicon could reduce the toxicity of aluminium for fish, because hydroxyaluminosilicate compounds prevent the absorption of aluminium. In a study of five men, Edwardson et al /10/ showed that gastrointestinal absorption of aluminium from orange juice is reduced if sodium silicate is added to the beverage. From these studies, two hypotheses may be proposed. The first was suggested by Birchall and Chappell /11/ who pointed out that the aluminium and

silicon concentrations in drinking water generally are negatively correlated. Thus, silicon may be a confounding factor in the statistical association observed between aluminium in drinking water and AD. Taylor et al /12/ showed a significant inverse correlation between soluble silicon and soluble aluminium ($r=-0.43$, $p<0.001$). Moreover, silicon from drinking water could be an important part of daily silicon intake and in a form particularly available for association with aluminium. Thus, Birchall and Chapell /11/ suggested as a second hypothesis that the association between aluminium levels in drinking water and Alzheimer's disease might be a consequence of the protective effect of silicon in water. Silicon in water might protect against the effect of dietary aluminium intake, and not only from aluminium in water. More specifically, Exley and Birchall /13/ suggested that concentrations of silicic acid above 100 µmol/l may prevent the absorption of aluminium from the gastrointestinal tract and facilitate its excretion by the kidney.

The literature is abundant on this topic, and several reviews have already been published /14,15,16/ exposing both positive and negative associations between aluminium and AD. The present paper reviews the epidemiological studies which have been conducted until now by distinguishing the different health effects of aluminium or silica: on neurological disorders (other than cognitive decline and AD), on cognitive decline and on dementia or Alzheimer's disease. For each health effect we have tried to separate the different sources of exposure to aluminium: water, occupational exposure, aluminium-containing products (like drugs or antiperspirants) and other sources of exposure.

2 Neurological disorders other than cognitive decline or AD

2.1 Water

Dialysis encephalopathy is not AD but is a "model" in that when a large quantity of Al comes into the blood from water, then part of it may cross the Blood Brain Barrier (BBB) and cause lesions which have some similarities with AD lesions /8,16/.

Dialysis encephalopathy is one of the main observations in favor of the neurotoxicity of aluminium. Studies /17,18/ have strongly implicated the high concentration of aluminium in tap waters used to prepare the dialysate and which can pass into the bloodstream. Perazella and Brown /19/ reported a case of a patient with renal failure following a bone marrow transplantation who developed an acute encephalopathy from apparent aluminium intoxication following intravesical aluminium. After the discovery that Al from the dialysate caused encephalopathy, the exposure of such patients to Al was greatly reduced and dialysis

encephalopathy has became relatively rare. Nakamura et al /20/ recently described a case with acute encephalopathy during dialysis and successfully treated with deferoxamine. The symptoms associated with acute aluminium toxicity appear to be reversible with deferoxamine, which is recognized as an effective chelator of aluminium /21/.

2.2 Aluminium-containing products

Alfrey et al /8/ measured aluminium levels in bone, muscle and brain in 10 control subjects, 9 uremic patients on dialysis and 12 uremic patients with the encephalopathy syndrome on dialysis. All dialyzed patients had received oral aluminium-hydroxide gels to control phosphate levels. High levels of aluminium were found in tissues and particularly in the grey matter of the brain of patients dying from this encephalopathy syndrome. The grey-matter Al content was 2.18 in controls, 6.50 (not significant) in the uremic group on dialysis and 24.98 in the patients with encephalopathy ($p<0.01$ versus control and $p<0.01$ versus uremic). In that study the aluminium content of the water used for the preparation of the dialysate was repeatedly measured and was negligible.

More recently, Roberts et al /5/, showed that serum (mean ± 1 s.d., 0.54 ± 0.17 μmol/l) and urine (5.03 ± 2.68 μmol/l) aluminium concentrations were significantly raised for patients aged 39-70 years with peptic ulcer/dyspepsia on regular aluminium hydroxide therapy for at least 6 months compared with healthy volunteers aged 30-65 years (respectively, 0.21 ± 0.13 μmol/l, 0.95 ± 0.82 μmol/l).

Reusche et al /22/ recently reported the fatal aluminium-encephalopathy of a patient after a reconstructive otoneurosurgery, for whom bone reconstruction was performed with an aluminium-containing cement.

2.3 Occupational exposure

Workers in refineries or smelters may be exposed to aluminium in the form of dusts, fumes and/or skin contact. Benke et al /23/ reviewed the different specific chemical exposures and exposure assessment methods relating to epidemiological studies in the aluminium industry. Since it has been shown that aluminium dust may reach the central nervous system via the nasal olfactory pathway /24/, several epidemiological studies have been undertaken to examine the potential relationship between aluminium exposure in the workplace and the risk of neurological disorders. The idea of a neurotoxic effect of aluminium with occupational exposure began with a fatal case of encephalopathy associated with inhalation of aluminium dust /25/.

2.4 Other types of exposure

A further link between aluminium and neurodegenerative disorders has been found in areas of the Western Pacific such as the island of Guam, which has unusual soils with high amounts of aluminium and low amounts of magnesium and calcium. The inhabitants are particularly prone to amyotrophic lateral sclerosis or Parkinsonism with dementia and in either case the brains of affected subjects show neurofibrillary tangles like those of AD /26/.

3 Cognitive functions

3.1 Water

A description of the different epidemiological studies on the relationship between Al and cognitive functions is given in Table 1. Two studies from Britain and Switzerland, Wood et al /27/ and Wettstein et al /28/, did not find any relationship between impaired cognitive function and aluminium exposure in drinking water. Wettstein compared the degree of mental impairment in old residents (81-85 years) in two parts of a town with different levels of aluminium in their drinking water. The mean scores of the tests (using two simple subtests of the variant Zurick Mini Mental Status Tests) in the low and in the high district were almost identical. The failure to detect any relationship was perhaps due to the fact that only two drinking water sources were investigated and that the highest concentrations of aluminium that were measured in these waters were about 0.1 mg/l. It may be that other water components or other characteristics of the geographical area influenced the relationship between aluminium and AD. It is thus important to include diverse geographical areas in epidemiological studies.

More recently a case-control study /29/ was undertaken in Camelford (South England) following an incident occurring in 1988 which contaminated the water supplies with 20 tons of aluminium sulphate used in the treatment of drinking water. Three years after the incident, an investigation was conducted to examine 55 self-selected adults (30 women and 25 men, aged 15-70 years, mean 41.8 (2.1) years), who complained of short-term memory loss and impaired concentration. They were compared to 15 siblings nearest in age to one of the group but who had not been exposed to the contaminated water. The results showed that the Camelford participants exposed to aluminium had lower psychomotor performances than their controls.

However, several shortcomings in the «design» of the study must be pointed out. The inquiry examined only a small number of exposed and non-exposed subjects. Moreover, the population was self-selected according to the cognitive impairment and was certainly not representative of the local population. Thus, the results of psychomotor testing were probably influenced and biased by the participants who considered themselves as victims of this incident. Nevertheless, the results found on the visual evoked potential test, which is an objective test, are probably resistant to bias caused by litigation.

A series of papers /30,31,32/ presented the results of the Ontario Longitudinal Study of Aging (LSA) whose participants were followed up for about 30 years. They reported, for example, an odds ratio of 2.72 ($p<0.01$) for subjects in areas where the fluoride water concentrations were relatively low (<0.88 mg/l) and the Al concentrations relatively high (>0.085 mg/l), compared with subjects in areas where the fluoride concentrations were high and the Al concentrations low /31/.

In an analysis of the Paquid sample, a weighted mean measure of exposure to aluminium was computed using results of two surveys conducted in 1991. To evaluate the past exposure of the subjects, a history of the water distribution network over the previous 10 years (1981-1991) was established. The results of the Paquid cohort /33/ reported an association of baseline cognitive impairment (defined as a score of less than 24 on the Mini-Mental State Examination) with aluminium, pH and calcium (negatively associated). Some of these results were difficult to explain; aluminium was positively associated when the pH was less than 7.3 and negatively associated when the pH was higher. Several investigators have reported that the pH of drinking water could affect the solubility of aluminium components and the type of aluminium containing species that are formed. It is plausible that the biological availability of aluminium is higher at low than at high pH, which could lead to an interaction between pH and aluminium. Forbes et al /32/ found that at neutral pH, relatively low aluminium concentrations and relatively high fluoride concentrations decreased the odds of exhibiting cognitive impairment by a factor of about five, compared with other types of drinking water.

More recently, we evaluated in the Paquid cohort the association between aluminium in drinking water and the evolution of cognitive functions measured by the Mini-Mental State Examination (MMSE) score, a major predictor of dementia /34/. This analysis had two main methodological focuses. First, the evolution of the MMSE score is known not to be sensitive to diagnostic errors that may be present in the detection of demented or Alzheimer's disease cases. Second, cognitive decline is thought to precede by 3-5 years the occurrence of dementia and is less subject to competitive morbidity or mortality. This analysis suggested

that cognitive decline with time may be related to high concentrations of aluminium (>0.1 mg/l) or low concentrations of silica (<11.25 mg/l) in drinking water.

3.2 Occupational exposure

Chronic exposure to aluminium and its possible neurotoxicity were also reported in a study of 607 Canadian gold miners exposed to McIntyre aluminium powder used as a prophylactic agent against silicosis /35/. The exposed miners were almost two times more cognitively impaired than the unexposed miners. The length of treatment ranged from 6 months to 36 years and the proportion with impaired cognitive function increased progressively with duration of treatment. This topic is reviewed by several papers /14,2,36,37/ and no clear-cut trends have yet emerged. Most of the epidemiological studies have failed to establish clear exposure-response relationships between specific workplace chemicals and neurological disorders. Akila et al /38/ reported cognitive impairment in aluminium welders in Finland that seemed proportional to urine concentrations of aluminium. Nevertheless, Letzel et al /39/ did not find any cognitive decline after a chronic exposure to aluminium dust in workers of a powder-producing plant.

4 Dementia and Alzheimer disease

Moore et al /40/ recently compared the gastrointestinal absorption of Al under normal dietary condition using ^{26}Al tracer, for 13 AD patients and 13 age-matched controls (aged 62-76 years). The mean fraction of Al absorbed by AD subjects exceeded controls by a factor of 1.64 ($p<0.05$). Roberts et al recently compared the excretion of aluminium for 8 demented patients with 114 control subjects, all with a normal dietary intake. They showed that patients with dementia had elevated Al concentrations in both blood (mean in µmol/l ± 1 s.d., 0.66 ± 0.2) and urine (2.84 ± 1.68) compared with healthy volunteers (respectively, 0.21 ± 0.13, 0.95 ± 0.82). However this study, which had insufficient data for the control group aged over 65 years, could not conclude whether this was a phenomenon of dementia or a consequence of aging. The data also showed that the urine silicon concentrations were significantly different in the urine of the demented group compared with the control group (mean in µmol/l ± 1 s.d., 1587 ± 645 and 471 ± 322), respectively. This suggests that an increased silicon excretion in dementia might be associated with an increased aluminium excretion, possibly through the formation of aluminosilicates.

4.1 Water

A synthesis of the different epidemiological studies on Al and dementia is described in Table 2 and Table 3. Most of the epidemiological studies have focused on the association between aluminium in tap water and AD, despite the fact that this source of exposure represents a relatively minor proportion of intake compared with other dietary and non-dietary sources. Less than 5 percent of the daily intake of aluminium has been reported to come from aluminium in public water supplies /41/. Nevertheless, data on aluminium in drinking water are relatively available and it is widely thought that aluminium in drinking water is more bioavailable, i.e. more readily taken up from the gut into the bloodstream than aluminium from food. Furthermore, when exposed to drinking water with a high concentration of Al, a much lower quantity of Al is able to cross the BBB, the effect of which could be simply to accelerate an Alzheimer pathological process which may have already started.

Most of the studies were ecological in design in that they studied the relationship between rates of Alzheimer's disease in a geographical region and the concentration of aluminium in drinking water. The most widely publicized and the first one was that of Martyn /42/. Cases of dementia between 40 and 69 years of age and ascertained from the records of seven CT scanning units were studied. Patients with dementia were classified into four categories according to clinical information (probable AD, possible AD, cerebrovascular dementia and dementia from other causes). Rates of disease were age-standardized to the 40-69-year-old population of England and Wales. Mean aluminium concentrations in water supplying the 88 country districts of the study were estimated over the previous 10 years. The results showed a significant association for probable AD with a relative risk (RR) equal to 1.5 (1.1-2.2) for high (>0.11 mg/l) as compared to low aluminium concentrations (>0.01 mg/l). However, there was no dose-response effect of aluminium.

Furthermore a series of population studies has been done using death certificates /43,44,45,46/. Age-adjusted death rates were calculated on the basis of the total number of death certificates from dementia or AD. These studies also reported a significant relationship between aluminium concentration in drinking water and the occurrence of AD. However, it must be noted that dementia is not always recognized as a distinct disease and recorded on death certificates. This can often lead to an underestimation of mortality rates, and probably to biases if the diagnosis of AD in certain regions is more easily recorded than it is in others.

Several case-control studies have also been done. The largest case control study was carried out in the province of Ontario by Neri and Hewitt /47/. They compared 2232 patients aged 55 years and over who had

been discharged from an Ontario hospital with a diagnosis of Alzheimer's disease or presenile dementia with the same number of controls matched for age and sex and discharged with a non-psychiatric diagnosis. The results showed a relative risk of 1.46 ($p<0.05$) for AD or presenile dementia for subjects living in areas where the drinking water aluminium concentration was greater than 0.200 mg/l (compared to < 0.01 mg/l). More recently, Mclachlan /48/ compared 119 autopsy-verified cases of AD with 51 controls, but focused on the residential histories for estimating aluminium exposure. Using aluminium concentration of public drinking water at last residence before death as the measure of exposure, the odds ratio (OR) for AD to all controls was 1.7 (95% CI 1.2-2.6). Estimating aluminium exposure from a 10-year weighted residential history resulted in estimates of OR of 2.5 (95% CI 1.2-5.3) for a cutoff value of 0.1 mg/l of aluminium. Even though they found a tendency for a relationship between Al in tap water and AD, this association was not significant. Two recent British studies failed to find any relationship between AD and aluminium in drinking water /49,50/. The study of Forster /49/ with a modest statistical power (109 cases vs 109 controls) did not find any association with aluminium in drinking water related either to a person's main place of residence 10 years before dementia onset or to birthplace. Martyn et al /50/ also carried out a case-control study in which they assessed exposures from historical measurements of aluminium in water supplies. There was no tendency for an increased risk with aluminium concentration either when aluminium levels were averaged from age 25 years to diagnosis, from age 25 years to 10 years before diagnosis, or over 10 years before diagnosis. The association was in fact the inverse. The inconsistency of these results with those of other studies may be explained not only by methodological problems (such as the number of subjects enrolled) but also by the fact that the above mentioned studies examined younger subjects (aged 43-75 years), so they examined presenile rather than senile dementia of Alzheimer type.

The effect of aluminium in drinking water on the risk of AD was examined in a large prospective cohort (Paquid), including 3,777 subjects aged 65 years and over and living at home in 75 civil parishes in Southwestern France in 1988-1989. The first results /51/ obtained on 40 prevalent cases of probable AD among a sub-sample of 2,792 subjects showed a significant linear association (RR=4.53 (3.36-6.10), for a difference of 0.1mg/l between the two values compared). However, this was based on retrospective measures of the aluminium concentrations that were not reliable; in particular some of these measures were old, and sampling and measurement techniques have changed in recent decades. Results obtained on incident cases of AD after 8 years of follow-up were recently published /52/. In this study, additional results of chemical analyses of drinking water carried out by the sanitary administration between 1991 and 1994

were used to evaluate exposure to aluminium. The sample studied included 2,698 non-demented subjects at baseline, for whom components of drinking water and covariates were available. A total of 253 incident cases of dementia (with 17 exposed to high levels of aluminium) including 182 AD (with 13 exposed to high aluminium levels) were identified. The relative risk of dementia adjusted for age, gender, educational level, place of residence and wine consumption was 1.99 (95% CI 1.20-3.28) for subjects exposed to an aluminium concentration greater than 0.1 mg/l (a threshold already used in previous studies /42,48/). A similar result was found specifically for AD (adjusted RR = 2.14, 95% CI 1.21-3.80). However, no dose-response relationship was found.

Recent epidemiological results on the Paquid cohort /52/ after 8 years of follow-up have shown that high silica levels (≥11.25 mg/l) are associated with a lower risk of dementia and Alzheimer's disease (respectively, adjusted RR = 0.74, 95% CI 0.58-0.96 and adjusted RR = 0.73, 95% CI 0.55-0.99). These results are concordant with the hypothesis of Birchall and Chapell /11/. If this assumption is true, the exact risk attributable to aluminium is probably underestimated in the Paquid cohort, which does not consider total daily aluminium intake (which is difficult to measure). However, results obtained by Martyn et al /50/ in a case-control study did not support a protective role of silicon.

Gauthier et al /53/ have assessed the relationship between long-term exposure to dissolved aluminium forms and AD development using a case-control study (68 cases) in Quebec. AD was diagnosed using the NINCDS-ADRDA criteria /54/. Potential individual long-term exposure to aluminium forms in drinking water was assessed by combining the subject's residential history (from 1945 onwards) with the physicochemical data of the municipalities. In contrast with earlier studies, this case-control study included information on genetic characteristics of the subjects and aluminium speciation in water (in addition to educational level). The data concerned total aluminium, total dissolved aluminium, monomeric organic Al, monomeric inorganic Al, polymeric Al, Al3+, and complexes of Al with hydroxide, fluoride, silicon and sulfate. No significant association was observed between long-term exposure to Al total (> 0.077 mg/l) and AD (odds ratio 1.52; 95% CI 0.59-3.88) nor with the exposure estimated at onset (odds ratio 2.10; 95% CI 0.83-5.35). Nevertheless, exposure to organic monomeric Al (> 0.012 mg/l, estimated at the onset of the disease) was significantly associated with AD (odds ratio 2.67; 95% CI 1.04-6.90). This relationship between monomeric Al and AD was significant only after adjustment for the genetic characteristics (presence of the ApoE ε4 allele and cases of dementia or AD among first-degree relatives). No relation between hydroxialuminosilicates or silicic acid and AD was observed.

Iron concentrations are also of interest because compounds like transferrin are thought to be involved in the transport of aluminium to the brain /55/ and iron and aluminium compete for binding with these molecules. In a multivariate analysis, Forbes et al /56/ found a relationship between the level of iron in tap water and the risk of AD reported on death certificates for persons over the age of 85.

4.2 Aluminium-containing products

The regular ingestion of aluminium-containing antacids represents a major source of exposure to aluminium. However, very few studies have related their use to the development of AD. Two case-control studies have explored this association /57,49/. Forster et al /49/ obtained an Odds Ratio equal to 1.6 (95% CI 0.77-3.51) for prolonged (6 months) antacid users, but this association was not significant. The results of Graves et al /57/ were surprising; in a case-control study of 130 matched pairs, the adjusted OR for AD was 3.1 (95% CI 1.3-7.5) when considering all antacids, and a dose-response gradient was found. However, when only aluminium-containing antacids were analyzed, the overall adjusted OR was only 0.7 (95% CI 0.3-2.0). The data of a long-term mortality follow-up study of 9,928 patients did not suggest that these patients, who may be presumed to have ingested large amounts of antacids containing aluminium, were at greater risk of AD /58/.

Aluminium salts are the major constituent of many widely used antiperspirant products, and the possibility that antiperspirant aluminium might exert an effect on health should not be ignored /59/. Experiments on mice have shown that aluminium salt could pass the skin barrier, and the transdermal uptake of aluminium resulted in the accumulation of aluminium in the hippocampus of the mouse brain /60/. However, in the epidemiological field, little consideration has been given to the effect of use of antiperspirants with aluminium and the risk of AD. To our knowledge, only one epidemiological study has revealed an increased risk of AD for subjects using aluminium-containing antiperspirants /57/.

Epidemiological studies on aluminium exposure from food are uncommon, probably due to the difficulties of measuring such exposure. In a recent preliminary case-control study (23 AD cases versus 23 controls matched by age, gender and date of admission to the center), Rogers and Simon /61/ examined the association between consumption of food containing aluminium additives and the risk of Alzheimer's disease. Next-of-kin for patients with AD and controls completed an interview on the subject's medical history, lifestyle habits and dietary history (using the Health Habits and History Questionnaire), so the use of aluminium-containing food could be ascertained over a five-year period preceding the diagnosis for cases

and the same period for controls. Consumption of food with a high aluminium content, at least once per day, yielded a crude OR of 2.0 and an adjusted OR of 8.6, but this association was not significant (p=0.19). No clear association was found with the consumption of tea, although tea infusions are a potentially important source of dietary aluminium. In a case-control study Forster et al /49/ found an elevated odds ratio (OR=1.4, 95% CI 0.81-2.63) with tea consumption (> 4cups/day), but this association was not significant.

4.3 Occupational exposure

No evidence has been obtained that long-term aluminium exposure in the workplace leads to dementia and AD. Three recent case-control studies did not find any association between workers in contact with aluminium dust and fumes, and AD /62,63,64/. The inconsistency in these data may be due to differences in exposure assessment. Namely, subjects are often exposed to several potential toxicants other than aluminium, making it difficult to identify the role of aluminium in the occupational environment. Furthermore, most of the studies are based on a small number of subjects.

4.4 Other types of exposure

Significant amounts of aluminium may also be supplied from aluminium cooking utensils, although this exposure has attracted less attention. The bioavailability of aluminium in cookware is unclear, even if it is known that such utensils may release aluminium when used to cook acidic food /65,66,67/. Aluminium might be more bioavailable when dissolved in water than in foodstuffs. In a prospective study /52/, no influence was found with the use of aluminium cookware on the risk of dementia (RR=1.04, p=0.86).

5 Conclusion and perspectives

The most solid results have been obtained with dialysis encephalopathy in which Al might be a causal agent. However, the link between Al in drinking water and cognitive impairment or AD is still controversial, with a mixture of positive and negative epidemiological results. The role of silica in drinking water has been less studied from an epidemiological point of view, and there are no clear results.

At present Alzheimer's disease is known to be a complex multifactorial pathology involving genetic and environmental components. It is known that several genetic mutations at several loci (mutations on

presenilins on chromosomes 1 and 14, mutations of the APP gene on chromosome 21) are linked with a hugh probability of the onset of Alzheimer's disease, and that the presence of the ε4 allele on the APOE gene (on chromosome 19) is linked with an increased incidence of the disease. Moreover, other susceptibility genes may remain to be discovered. Epidemiological studies have also shown that several factors like age, gender, educational level, consumption of wine or tobacco modify the risk of developing of the disease. Gene-environment interactions should also be studied. It may be that only a fraction of the population is susceptible to Al toxicity. Transferrin is the major transport protein for both iron and Al in blood. Farrar et al /55/ have suggested that the binding of Al to transferrin is reduced in AD patients. They proposed that such patients might have higher levels of non-transferrin-bound low-molecular weight Al complexes in their plasma, which might more readily cross the blood-brain barrier. Furthermore, the transferrin variants C1 and C2, accounting for the majority of the population in all races, have already been explored. The results of Namekata et al /68/ on 291 controls compared to 294 AD suggested that the C2 allele frequency in AD patients homozygous for the APOE ε4 allele is markedly increased, as in the remaining AD patients carrying zero or one copy of the ε4 allele. The C2 allele may predispose ε4 homozygotes to AD. However, contrasting results were recently obtained by Hussain et al /69/. Future assessment of the relationship between Al exposure and AD should thus include study of the genetic characteristics of subjects.

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Table 1: Epidemiological studies of aluminium and cognitive impairment

Study	Design	Age	Diagnosis	Exposure	Association with aluminium
-Rondeau, 2001 France	Cohort (3401)	(65 and over)	Psychometric tests	water	+
-Letzel, 2000 Germany	Population study 32 exposed, 30 non-exposed	(26-60 years)	Psychometric tests	occupation	-
- Altmann, 1999 UK	Retrospective study 55 exposed, 15 non-exposed	(15-70 years)	Clinical and Psychological tests	water	+
- Akila, 1999 Finland	Population study 28 reference, 27 low, 24 high exposure	(22-58 years)	Psychological tests	occupation	+
-Forbes, 1994 Canada	Case-Control,199 cognitive impairment, 286 controls	(75 and over)	Psychometric tests	water	+
-Jacqmin-Gadda, 1994, France	Population study (3697), 906 cognitive impairment	(65 and over)	Psychometric tests	water	+/-
- Wettstein, 1991 Switzerland	Population Study (805)	(81-85 years)	Psychometric tests	water	-
- Rifat, 1990 Canada	Retrospective study 261 exposed, 346 non-exposed	(60-70 years)	Psychometric tests	occupation	+
- Wood, 1988 UK	Population study (386)	(55 and over)	Psychometric tests	water	-

Table 2: Epidemiological studies of aluminium and AD or dementia

Study	Design	Age	Diagnosis	Exposure	Association with Aluminium
- Gauthier, 2000 Canada	Case-control, 68 AD		Clinical diagnosis	water	+
- Rondeau, 2000 France	Cohort (2698 subjects) 253 demented, 182 AD	(65 years and over)	Clinical diagnosis	Water	+
- Moore, 2000 UK	Case-Control, 13 AD, 13 controls	(62-76 years)	Clinical diagnosis	GA*	+
- Graves, 1998 USA	Case-control 89 AD, 89 controls		Clinical diagnosis	occupation	-
- Martyn, 1997 UK	Case-Control, 106 AD, 441 controls	(42-75 years)	Clinical diagnosis, Computerized tomographic records	water	-
- Gun, 1997 Australia	Case-control 170 AD, 170 controls	(52-96 years)	Clinical diagnosis	occupation	-
- McLachlan, 1996 Canada	Case-Control, 119 AD, 51 controls		Autopsy	water	-
- Forbes, 1996 Canada	Population Study (1041) AD	(85 and over)	Death certificates	water	+
- Salib, 1996 UK	Case-control, 198 AD, 164 other dementia, 176 non-demented		Clinical diagnosis	occupation	-

GA*: gastrointestinal absorption

Table 3: Epidemiological studies of aluminium and AD or dementia (to follow)

Study	Design	Age	Diagnosis	Exposure	Association with Aluminium
- Forster, 1995 UK	Case-Control, 109 PDAT, 109 controls	(< 65 years)	Clinical diagnosis	water antacid	- -
- Taylor, 1992 UK	Case-Control, 20 AD, 20 controls	(65-89 years)	Clinical diagnosis	GA*	+
- Neri, 1991 Canada	Case-Control, 2232 AD or presenile dementia, 2232 Controls	(55 and over)	Death Certificates	water	+
- Michel, 1991 France	Population study (2792), 66 demented, 51 AD	(65 and over)	Clinical diagnosis	water	+
- Frecker, 1991 Canada	Population study (568345) 379 demented		Death Certificates	water	+
- Flaten, 1990 Norway	Population study (14727) 586 demented		Death Certificates	water	+
- Graves, 1990 USA	Case-control 130 AD, 130 controls	(55 and over)	Clinical diagnosis	Antacid antiperspirant	+/- +
- Martyn, 1989 UK	Population study 1185 demented, 666 AD	(40-69 years)	Computerised tomographic scanning	water	+
- Vogt, 1986 Norway	Population study		Death certificates	water	+

GA* : gastrointestinal absorption