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Relationship between aluminum and silica concentrations in drinking water and Alzheimer's disease: an 8-year follow-up study

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Abstract

To investigate the effect of aluminum and silica in drinking water on the risk of dementia and AD the authors analyzed data from a large prospective cohort (Paquid) including 3,777 subjects aged 65 years and over, living at home in 75 civil parishes in Gironde and Dordogne in southwestern France. The subjects were followed up for eight years with an active search for incident cases of dementia or AD. Mean exposure to aluminum and silica in drinking water was estimated in each area. We analyzed 2,698 non-demented subjects at baseline, and for whom components of drinking water and covariates were available. 253 incident cases of dementia including 182 AD were identified. The relative risk of dementia adjusted for age, gender, educational level, place of residence and wine consumption was 2.03 (95 percent CI 1.23-3.34) for subjects exposed to aluminum concentration greater than 0.1 mg/l. This result was confirmed for AD (adjusted relative risk=2.20, 95 percent CI 1.24-3.89). Inversely, the adjusted relative risk of dementia for subjects exposed to silica (≥ 11.25 mg/l) was 0.75 (95 percent CI 0.58-0.96). These findings support the hypothesis that aluminum in drinking water is a risk factor for AD.

Key words: aluminum; Alzheimer's Disease; dementia; drinking water;
silica

Although much effort has been devoted to identifying the genetic determinants of Alzheimer's disease (AD),¹ it is likely that certain environmental factors play a role in this disease. Because of its proven neurotoxicity, aluminum may be one such factor. Although the hypothesis of a link between aluminum and AD has been supported by several biological findings,²⁻⁵ uncertainty still prevails. Dialysis encephalopathy⁶ is one of the main observations in favour of the neurotoxicity of aluminum because it proves that aluminum is able to reach the brain and induce neurofibrillary degeneration and neuronal death. Several epidemiological studies have reported an association between exposure to aluminum and dementia, most studying aluminum from drinking water,⁷⁻⁹ but some from other sources.^{10,11} Another hypothesis has been proposed by Birchall^{12,13} on the role of silicon in water as a protective factor against aluminum toxicity. However, there is much controversy regarding these findings and their interpretation, in particular owing to recently published epidemiological studies which failed to find an association.^{14,15}

In previous papers^{16,17} we have shown that baseline cognitive performances of subjects in the Paquid cohort were correlated with levels of aluminum and silica in drinking water. Here we present results for incident

dementia and Alzheimer's disease based on 8 years of follow-up.

MATERIALS AND METHODS

Sample

The Paquid cohort was designed to study prospectively a representative random sample of 3,777 people aged 65 years or older at baseline, and living at home in one of 75 randomized rural or urban parishes of the administrative areas of Gironde or Dordogne. Subjects were randomly selected from electoral rolls and baseline data were collected in 1988-1989. Subjects were then re-evaluated 1, 3, 5 and 8 years after the initial visit to diagnose incident cases of dementia. The general methodology of Paquid has been described fully elsewhere.^{18,19}

Measure of dementia and AD

In brief, prevalent and incident cases of dementia were detected by a two-step procedure. First, all participants underwent a 1-hour home interview and a psychometric evaluation with a trained psychologist who systematically completed a standardized questionnaire designed to obtain the A (memory impairment), B (impairment of at least one other cognitive function) and C

(interference with social and professional life) criteria for dementia according to the DSM-III-R.²⁰ Second, subjects positive for these criteria were examined by a senior neurologist who confirmed the diagnosis and applied the NINCDS-ADRDA²¹ criteria for AD and the Hachinski score for vascular dementia²² to document the diagnosis of dementia and its etiology: probable or possible AD or other type of dementia.

Measure of exposure

A specific study (ALMA) was started in 1990 to examine the relationship between aluminum in drinking water and Alzheimer's Disease for the Paquid subjects. After investigation of the water distribution network, the sample was divided into 78 drinking water areas. Two surveys were carried out in 1991 to measure pH and concentrations of aluminum, calcium, and fluorine in each water supply, and to study the variability of the measurements. These data were described in detail by Jacqmin *et al.*¹⁶ Then all the results of the chemical analyses of drinking water (including silica) carried out by the sanitary administration between 1991 and 1994 were collected. Therefore, for each drinking water area, we computed a weighted mean of all the measures of each drinking water component. The weighting took into

account the length of the period of use of each water supply over the previous 10 years (1981-1991) and the relative contribution of each water supply. The present study is based on 70 areas for which measurements were available.

Statistical analysis

A Cox proportional hazard model with delayed entry²³ was performed to estimate relative risks (RR) and to adjust for covariates. Age was taken as the basic time scale in the analysis, so that the risk of dementia or AD at a given age could be modelled. For the analyses we considered only subjects free of dementia at entry into the cohort. In a previous analysis²³ we observed that the proportional hazards assumption was violated for gender, so we chose to perform a stratified analysis.²⁴ The main risk factors under consideration were aluminum as a quantitative variable or as a binary variable with the threshold of 0.1 mg per liter already used in previous studies,^{7,9} and silica as a binary variable with 11.25 mg/l (the median in our sample) as the cut-off. We adjusted for potential confounders: educational level (with vs without a primary school diploma),²⁵ wine consumption (non-drinkers or mild drinkers vs moderate or heavy drinkers)²⁶ and place of residence (rural vs urban). Adjustment for baseline cognitive status measured by the Mini

Mental State Examination (MMSE)²⁷ scores was done in a complementary analysis (MMSE was available for 2,658 subjects).

We then examined separately the effect of mineral water consumption (daily consumption of mineral water vs no or occasional consumption). This information was collected only at the 3-year follow-up visit. Thereafter, we examined the sub-sample of non-demented subjects who were visited at that follow-up, and we used incident cases of dementia between the 3-year and 8-year follow-up visits.

RESULTS

Among the 3,777 subjects who initially agreed to participate, 3,675 were non-demented at the first visit. The measurements of water and adjustment covariates were available for 3,401 subjects unaffected at the initial visit. Among the 3,401 subjects, 703 (20.6 percent) did not participate in the follow-up because they had died (n=383, 11.3 percent), were lost to follow-up (n=4, 0.1 percent) or refused the follow-up procedure (n=316, 9.3 percent). At least one complete follow-up evaluation was performed in 2,698 subjects (79.3 percent). The percentage of deaths before the investigation between exposed and non-exposed to aluminum subjects (13.9 percent vs 11.2 percent,

p=0.42) were not significantly different; nor refusals (12.7 percent vs 9.3 percent, p=0.27).

At baseline, 91 percent of the individuals had stayed more than 10 years in the same parish, and the mean length of residence in the same parish was 41 years. During the 8-year follow-up of these subjects, 253 subjects were diagnosed with dementia and 182 (72.0 percent) were classified as having Alzheimer's disease (probable or possible). The incidence rate for all causes of dementia and Alzheimer's disease was estimated as 1.69 per 100 person-years and 1.22 per 100 person-years, respectively.

Aluminum levels in water supplies ranged from 0.001 to 0.459 mg/l with a median value of 0.009 mg/l, and 63 subjects were exposed to more than 0.1 mg/l. Silica levels in water ranged from 4.2 to 22.4 mg/l and were inversely related to aluminum concentrations, but this negative correlation was weak in our study (Spearman rank correlation coefficient -0.18, $p = 0.13$).

The results of the analyses (table 1) suggest that the risk of dementia was higher for subjects living in parishes where the mean aluminum concentrations exceeded 0.1 mg/l than for those living in areas where concentrations were less than 0.1 mg/l (RR non-parametrically adjusted for age and gender 2.33, $p < 0.001$, model 1). Conversely, higher silica concentrations

(≥ 11.25 mg/l) were associated with a reduced risk of dementia (RR non-parametrically adjusted for age and gender 0.71, $p = 0.007$, model 2). After additional adjustment for educational level, wine consumption and place of residence, aluminum and silica concentrations remained associated with dementia (RR for aluminum 2.03, $p = 0.006$; RR for silica 0.75, $p = 0.023$, model 3). There was no significant interaction between aluminum and silica concentrations (likelihood ratio test 0.72, $p = 0.48$). Results of model 3 were not significantly changed after adjustment for baseline MMSE (RR for aluminum 2.08, $p = 0.005$; RR for silica 0.74, $p = 0.017$). The pH level was not associated with dementia and the interaction between aluminum and pH was not significant.

The observations are summarized in table 2. Although only 63 exposed subjects living in 4 parishes were followed up at least once, the number of observed cases was much greater than the number of expected cases. The expected number of cases using the Cox model²⁴ was computed to be 8.71 while 17 cases were observed.

Analyses restricted to cases classified as Alzheimer's Disease (182 cases) also showed a deleterious effect of high aluminum concentrations and a protective effect of high silica concentrations on the risk of AD (table 3). These

effects were not significant for other types of dementia (71 cases), although the relative risks were of the same order. This may be explained by a lack of power in the latter analysis.

Information about mineral water consumption was collected for 1,638 non-demented subjects seen at the 3-year follow-up and for whom covariates were available; 105 subjects developed dementia (including 88 AD cases) between the 3-year and the 8-year follow-up. In this sub-sample, 48 percent of the subjects were classified as daily drinkers of mineral water. The analysis of this subsample, adjusted for educational level, wine consumption, place of residence and silica yielded a relative risk of 2.89 (95 percent CI 1.51-5.52, $p < 0.001$) for aluminum $\geq 0.1\text{mg/l}$. This relative risk reached 3.36 (1.74-6.49, $p < 0.001$) after adjustment for mineral water consumption. This may be because most of the exposed subjects (69 percent) drank some mineral water daily versus only 47 percent in non-exposed subjects. There was no evidence of a significant interaction between aluminum and mineral water consumption. In this sub-analysis, after adjustment for educational level, wine consumption, place of residence and aluminum, the relative risk for silica was estimated to be 0.61 (0.41-0.91, $p = 0.016$). The effect of silica was not changed after adjustment for mineral water consumption (RR 0.61,

0.41-0.91, $p = 0.016$).

DISCUSSION

In this study, high aluminum levels in drinking water (≥ 0.1 mg/l) were associated with an elevated risk of dementia and AD. This result was highly significant despite the low number of subjects exposed to such levels. Inversely, high silica levels (≥ 11.25 mg/l) were associated with a lower risk of dementia and AD.

In separating aluminum concentrations into 4 classes, no tendency for a dose-response effect for aluminum was apparent, even though a significant linear relationship between aluminum and dementia was obtained (adjusted RR 1.3 for an increase of 0.1 mg/l, $p = 0.01$). However, the model with aluminum in two classes (table 1) was slightly better than that where aluminum was a continuous variable (Akaike criterion: 2719.9 vs 2721.0).

Subjects who refuse to participate in the follow-up or die are probably more likely to be demented. If the participation of these subjects were different in the exposed and non-exposed group, this could produce an “attrition” bias. In the present study, the percentages of deaths or refusals before the investigation were higher for exposed subjects to aluminum, but this difference

was not significant, which makes such a bias unlikely.

In the present study it is not to be excluded that relative risks can be strongly influenced by selection effects operating in the population. A number of differences between individuals may be unobserved, like genetic disposition, environmental factors which influence the event. This heterogeneity can induce selection effects in the population, because individuals with a high risk, the most frail, will experience the event early, leaving a selected population at risk, less frail than the original population. A new approach would be to analyze the data with a correlated-frailty model,²⁸ in which individual frailties are introduced, as random variables.

The Paquid survey design incorporates a grouping of the participants into parishes, and this may induce a correlation of the observations. It is thus not to be excluded that some unmeasured environmental factor shared by the members of the same parish could play a confounding role.

We adjusted for baseline cognitive status, which is highly predictive of dementia and AD. This measurement of global cognitive functioning was not a confounding factor.

In the analyses we considered as exposed all the subjects living in parishes with high levels of aluminum. An alternative was to consider subjects drink-

ing daily mineral water as non-exposed; the effect of aluminum still remained unchanged and was still significantly associated with dementia (RR 3.31, $p=0.04$).

Several investigators have described that the pH of drinking water could affect the solubility of aluminium-components;²⁹ it is plausible that the biological availability of aluminium is higher for low than for high pH, which means that high pH would be associated with low concentrations of bioavailable aluminium. These results were not confirmed in our study; nevertheless, 98.7% of the measures of pH were higher than 7 (range: 6.31-8.44).

Surface waters (lakes or rivers) are often treated with aluminum sulphate to induce flocculation and remove organic and other contaminants. Indeed, in the parishes in this study, the median of aluminum concentration was higher in surface waters compared with underground waters (0.023 vs 0.006 mg/l). However, no elevated incidence of dementia was found for subjects living in areas supplied by surface waters.

Significant amounts of aluminium may also be supplied from aluminium cooking utensils. We performed an additional analysis including the use of aluminium cookware as an explanatory variable, but no influence on the risk of dementia was observed (HR 1.04, $p=0.86$, results based on 1,586

participants who had answered this question at the 3-year follow-up).

Our results confirm the significant association of AD with exposure to aluminum previously reported in epidemiological studies.^{7,9} Nevertheless, two recent studies failed to find a relationship with aluminum in drinking water.^{14,15} The study of Forster¹⁴ had a modest statistical power with a small number of subjects (109 cases and 109 controls). Furthermore, the inconsistency of our results with those of Forster¹⁴ or Martyn¹⁵ might be explained by the fact that their studies examined younger subjects (43-75 years) than in the Paquid cohort, so they examined presenile rather than senile dementia of Alzheimer type. As suggested by Taylor,³⁰ it is plausible that there is an increase in aluminum absorption with age, so the effect of aluminum may be larger after 75 years than before. Moreover, genetic factors are more influential in the etiology of presenile dementia.

Using theoretical chemistry and biological examples, Birchall³¹ and others³² argued that the major role of silica is to interact with aluminum in such a way as to reduce the biological availability of all sources of dietary aluminum and not only of aluminum from drinking water. Our results are concordant with this hypothesis, since we found a protective effect of silica on dementia, and this independently of the aluminum concentration in drink-

ing water. If the assumption of Birchall is true, the exact risk attributable to aluminum is probably underestimated in our study, which does not consider total daily aluminum intake (which is difficult to measure). However, many authors have postulated that aluminum in drinking water may be more bioavailable than aluminum from other sources.

The present study suggests that aluminum may be one of the factors associated with dementia and especially Alzheimer's disease, even if the proportion of exposed subjects was low in our population. These results must now be investigated further, since simple measures could be taken to reduce such exposure in the elderly.

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TABLE 1. Deaths and refusals before the investigation in the 3,401 subjects eligible at baseline

	followed (%)	deaths (%)	refusals (%)	Total
Aluminum \geq 0.1 mg/l	63(73.3)	12(13.9)	11(12.8)	86(100)
Aluminum $<$ 0.1 mg/l	2635(79.5)	371(11.2)	309(9.3)	3315(100)
Total	2698(79.3)	383(11.3)	320(9.4)	3401

TABLE 2. Relative risks (95%CI) for dementia according to water aluminum and silica concentrations

Variable	RR(95% CI)	<i>p-value</i>
Model 1*		
aluminum ($\geq 0.1mg/l$ vs $< 0.1mg/l$)	2.33(1.42-3.82)	< 0.001
Model 2*		
silica ($\geq 11.25mg/l$ vs $< 11.25mg/l$)	0.71(0.56-0.91)	0.007
Model 3†		
aluminum ($\geq 0.1mg/l$ vs $< 0.1mg/l$)	2.03(1.23-3.34)	0.006
silica ($\geq 11.25mg/l$ vs $< 11.25mg/l$)	0.75(0.58-0.96)	0.023

* non-parametrically adjusted for age and gender

† non-parametrically adjusted for age and gender and parametrically adjusted for educational level, wine consumption and place of residence.

TABLE 3. Expected and observed cases of dementia according to aluminum exposure after 8-year follow-up of the 2,698 subjects

	Alu<0.1 mg/l	Alu≥ 0.1 mg/l
sample size	2635	63
observed number of demented subjects	236	17
expected number of demented subjects *	244.29	8.71

* expected number calculated with Martingale residuals, non-parametrically adjusted for age and gender and parametrically adjusted for educational level, wine consumption and place of residence

TABLE 4. Relative risks (95%CI) for Alzheimer’s Disease (182 cases) and for other types of dementia (71 cases) according to water aluminum and silica concentrations

Variable*	Alzheimer’s disease		Other types of dementia	
	RR(95% CI)	<i>p-value</i>	RR(95% CI)	<i>p-value</i>
aluminum ($\geq 0.1mg/l$ vs $< 0.1mg/l$)	2.20(1.24-3.89)	0.007	1.63(0.58-4.55)	0.350
silica ($\geq 11.25mg/l$ vs $< 11.25mg/l$)	0.73(0.55-0.99)	0.040	0.78(0.48-1.25)	0.300

* non-parametrically adjusted for age and gender and parametrically adjusted for educational level, wine consumption and place of residence.