A preliminary study of dietary aluminium intake and risk of Alzheimer's disease

Mary A. M. Rogers, David G. Simon

Department of Medicine, State University of New York Health Science Center, Syracuse, NY 13210, USA

Address correspondence to: M. A. M. Rogers. Fax: (+1) 315 464 8290. Email: rogersm@vax.cs.hscsyr.edu

Abstract

Background: epidemiological studies of Alzheimer's disease and aluminium intake have focused on aluminium in drinking water. There have been no studies investigating the relation between the disease and the consumption of foods containing large amounts of aluminium additives.
Objectives: to conduct a pilot study to determine whether dietary intake of aluminium additives differs in individuals with and without Alzheimer's disease.
Design: matched case–control study. Controls were matched to cases on age, gender and date of admission to the centre.
Setting: Syracuse, New York, USA.
Subjects: 46 participants comprising 23 matched sets.
Methods: residents of the Loretto Geriatric Center with and without newly-diagnosed Alzheimer's disease were selected. Next-of-kin were asked to complete information on the resident's medical history, lifestyle behaviour and dietary intake before admission to the centre. An expanded form of the Health Habits and History Questionnaire was used to determine dietary intake. Consumption of foods containing elevated levels of aluminium additives was compared between cases and controls.
Results: the crude odds ratio for daily intake of foods containing high levels of aluminium was 2.0 and, when adjusted for covariates, was 8.6 ($P = 0.19$). Intake of pancakes, waffles, biscuits, muffins, cornbread and/or corn tortillas differed significantly ($P = 0.025$) between cases and controls. Adjusted odds ratios were also elevated for grain product desserts, American cheese, chocolate pudding or beverages, salt and chewing gum. However, the odds ratio was not elevated for tea consumption.
Conclusion: past consumption of foods containing large amounts of aluminium additives differed between people with Alzheimer's disease and controls, suggesting that dietary intake of aluminium may affect the risk of developing this disease. Larger studies are warranted to corroborate or refute these preliminary findings.

Keywords: *aluminium, Alzheimer's disease, food additives*

Introduction

The hypothesis that aluminium exposure is aetiologically related to Alzheimer's disease has led to much debate. Ecological studies have suggested that concentrations of aluminium in drinking water of 0.10–0.20 mg/l may increase the risk of Alzheimer's disease with relative risks ranging from 1.35 to 2.6 [1–6]. All the epidemiological studies thus far, however, have ignored the greatest source of aluminium for the ordinary citizen: food. Estimates of average dietary consumption in adults in the USA are 7–9 mg per day [7]. Since aluminium additives are contained in specific widely-available processed foods, consumption of aluminium from food is much greater than from drinking water and, over a lifetime, may represent substantial exposure. For example, one pancake eaten for breakfast and one piece of cake for dinner may yield 15 mg of aluminium [8]. Consumption of 1 ounce (28 g) of American cheese and one baking-powder biscuit yields approximately 20 mg of aluminium [8].

As early as 1911 the danger of consumption of foodstuffs with aluminium additives was reported by William Gies [9]. He described experiments in humans showing the gastric solubility of aluminium compounds in bread made with alum baking powder, as

well as experiments showing the absorption and excretion of aluminium in dogs fed baking-powder biscuits. The experiments led him to conclude that alum baking powders should be prohibited "in the interest of conservation of the best of our natural resources—the public health" [9].

It is our contention that investigators thus far have missed the most important exposure to aluminium for the average person. Since aluminium is found in high quantities only in particular processed foods and there is considerable interpersonal variability in the consumption of these foods, there is an opportunity to investigate differences in intake among individuals. We conducted a pilot study to examine dietary differences in individuals with Alzheimer's disease and matched controls.

Subjects and methods

Subjects were selected from the Loretto Geriatric Center in Syracuse, NY, USA from March to November 1993. All individuals with newly-diagnosed Alzheimer's disease from 1990 to 1993 were considered eligible. The diagnosis of Alzheimer's disease was ascertained using the criteria specified by the Joint Working Group of the US National Institute of Neurological and Communicative Disorders and the Stroke and the Alzheimer's Disease and Related Disorders Association. Individuals with vascular dementia, a history of alcoholism, syphilis, vitamin B_{12} deficiency or abnormal thyroid function were excluded. Each case was matched to one control who also was a resident of the Loretto Geriatric Center and who had no medical history of dementia. Cases were matched to controls by age (within 2 years for 70% of the sets and within 5 years for all sets), gender and date of admission to the centre (within 6 months). Forty-six subjects participated in the study giving a total of 23 matched sets.

Next-of-kin who served as carers for those with Alzheimer's disease before admission to the centre were contacted. These were either spouses or daughters. The spouse or daughter then completed an in-person interview with a trained interviewer on the subject's medical history, lifestyle habits and dietary history. Next-of-kin of each control (spouse or daughter)

completed a similar interview. Efforts were made to match the type of respondent for each case–control pair, i.e. spouse–spouse, daughter–daughter. This was possible for 20 of the 23 matched pairs.

Spouses or daughters were interviewed about dietary intake of the patient using the Health Habits and History Questionnaire, which was first developed at the National Cancer Institute of the National Institutes of Health and has been extensively tested for reliability and validity [10]. Respondents were asked to recall usual dietary intake for the 5 years before the onset of Alzheimer's disease for cases and the same 5-year period for the matched control. The questionnaire was modified to include specific foods containing high levels of aluminium. The aluminium content of foods was obtained using information collected and reported by Pennington [8]. Pennington reported high levels of aluminium in specific products containing additives including: (i) biscuits, cornbread, muffins, pancakes and tortillas, (ii) cakes, cookies, pastry and doughnuts, (iii) American cheese, (iv) chocolate pudding and some chocolate candies and (v) chewing gum. Some spices (including table salt) and tea are also high in aluminium, although when tea is brewed, one cup may contain lower amounts, depending upon the type analysed. Some non-dairy creamers also contain aluminium additives.

This study was regulated by the institutional review board for human subjects at the State University of New York Health Science Center in Syracuse. All next-of-kin consented to participate according to protocol. Of the 25 case next-of-kin approached for participation, two refused. Of the 25 control next-of-kin contacted, one refused.

Initial descriptive characteristics of the subjects were investigated using SYSTAT (Evanston, IL, USA). Random error was assessed using paired t-tests and McNemar's test. Conditional logistic regression (EGRET, Seattle, WA, USA) was used to determine odds ratios (ORs) for Alzheimer's disease with adjustment for covariates.

Results

The characteristics of the cases and controls are listed in Table 1. The mean age of the subjects was 73 years,

Table 1. Characteristics of subjects with Alzheimer's disease and controls

Characteristic	Cases ($n = 23$)	Controls ($n = 23$)
Age, years (mean $\pm$ SD)	73.7 $\pm$ 8.4	73.1 $\pm$ 8.4
Gender (%male/%female)	22/78	22/78
Respondent (%daughter/%spouse)	65/35	78/22
Weight, pounds (mean $\pm$ SD)	142.1 $\pm$ 25.7	141.2 $\pm$ 25.3
Body mass index, kg/m^2 (mean $\pm$ SD)	24.4 $\pm$ 3.0	23.3 $\pm$ 3.1
Kilocalories/day (mean $\pm$ SD)	1910 $\pm$ 688	1864 $\pm$ 774

Table 2. Odds ratios for aluminium-containing foods and Alzheimer's disease

| Food category[a] | No. of discordant pairs | Odds ratio | | P value |
		Crude	Adjusted[b]	
Pancakes, waffles, biscuits, muffins, cornbread, corn tortillas	5/0	∞	∞	0.025
Doughnuts, cookies, cake, pastry	7/4	1.75	34.6	0.11
American cheese, mixed dishes with cheese	6/4	1.5	7.9	0.41
Chocolate pudding, chocolate milkshake or hot chocolate	2/2	1.0	77.7	0.24
Salt	4/2	2.0	47.5	0.26
Pepper	8/5	1.6	1.1	0.86
Tea (hot or iced)	4/7	0.6	0.7	0.69
Chewing gum	5/3	1.7	3.3	0.31
All high-aluminium food (above) combined	6/3	2.0	8.6	0.19
Foods stored/baked/cooked in aluminium containers	4/2	2.0	32.3	0.22

[a]For all high-aluminium food and for foods in aluminium containers, 1+ servings/day was compared with <1 (reference category). For salt and pepper, "always, often or sometimes" was compared with "seldom or never". For chewing gum, once per week or more was compared with less than once per week. For all other items (grain products, dairy and tea), ≥2 servings/week was compared with <2.
[b]Odds ratios were adjusted for kilocalories, body mass index, education and intake of vitamins A, C and E.

and 78% were women. Most of the respondents who supplied the dietary information were daughters. The mean weight and body mass index for cases (before the onset of Alzheimer's disease) and controls (during the same time interval as the case) were similar. Mean daily kilocalorie intake was slightly higher in cases than controls, although not significantly ($P = 0.833$).

There were no differences between the cases and controls with regard to a history of migraine headaches ($P = 0.683$), seizures ($P = 0.480$), depression ($P = 0.683$), cirrhosis of the liver ($P = 1.000$), hepatitis ($P = 0.480$) or other liver disease ($P = 1.000$). A history of heart disease was more prevalent in the controls (30%) than in the cases (13%), although the difference was not significant ($P = 0.289$). Likewise, controls were more likely to have high blood pressure (43%) than cases (26%), although the difference was not significant ($P = 0.386$). Cases were more likely to report a history of 'stomach ulcers' (17%) than controls (9%), but again this was not significant ($P = 0.683$).

The OR for a family history of Alzheimer's disease was 3.50 ($P = 0.118$). There was no association between a prior history of head injury or education (as measured by the highest grade of schooling completed) and Alzheimer's disease in this data set. There were no statistically significant associations between daily anti-oxidant intake (vitamins A, C and E, α-carotene, β-carotene, cryptoxanthin, lutein or lycopene measured as continuous variables) and Alzheimer's disease.

The crude and adjusted ORs for foods containing high concentrations of aluminium are listed in Table 2. Consumption of foods with a high aluminium content (all foods combined) at least once per day yielded a crude OR of 2.0 and an adjusted OR of 8.6. For most of the food categories listed, the ORs were elevated. However, the category including pancakes, waffles, biscuits, muffins, cornbread or corn tortillas was the

only one which reached statistical significance at the 0.05 level. The OR was infinity (5/0 discordant pairs) with $P = 0.025$. The OR was also very high (OR = 47.5) for salt consumption (always, often or sometimes *versus* seldom or never). Consumption of American cheese, grain-based desserts and chocolate desserts and beverages twice a week or more yielded adjusted ORs of 7.9 to 77.7. The ORs for usage of chewing gum and for storing/baking foods in aluminium containers were elevated as well. Adjusted ORs were not elevated for pepper or for tea.

Further adjustment of the ORs in Table 2 by a family history of Alzheimer's disease did not diminish the estimates of effect. In fact, the OR for aluminium (all foods combined) was 15.7 after adjustment, and the ORs for individual food categories ranged from 7.9 (American cheese) to 507.4 (salt), with the exception of tea which was not elevated (OR = 0.62). The OR for non-dairy creamer use was also elevated (4.9).

Use of aluminium-containing medications in the 5 years before diagnosis for cases and the same time period for matched controls was also ascertained. The medications were Bufferin, Amphojel, Mylanta, Alutab, Alu-Cap, Alternagel, Aludrox, Basaljel, Gaviscon, Wingel, Digel, Maalox, Rolaids and Riopan. The crude OR for aluminium drug use (any *versus* never) was 1.0. When adjusted for body mass index, a family history of Alzheimer's disease and a prior history of head trauma, the OR for aluminium drug use (any *versus* never) was 8.3 ($P = 0.22$).

Discussion

This study suggests that researchers looking for a connection between aluminium and Alzheimer's disease may have been ignoring the most important source of aluminium for the average person. There may

be an association between Alzheimer's disease and consumption of foodstuffs which contain aluminium additives. The small sample size, however, hampers any definitive conclusions. The ORs, particularly the adjusted ORs, were very unstable. Granted that this study has limited statistical power to rule out random error, the results imply that aluminium, as added to foods as anticaking agents, emulsifiers, thickeners, leaveners and stabilisers, may have long-term health effects.

Recall bias is unlikely to account for the ORs in Table 2 since few Americans know which foods contain high aluminium concentrations. The exception would be foods cooked or stored in aluminium containers, as media attention has been given to this hypothesis. Not all grain-based products contain aluminium; some manufacturers use other leaveners, anticaking agents or thickeners. For example, products sold under the Jiffy label did not contain aluminium additives during the time period in this study. Therefore, we excluded those individuals who used Jiffy pancakes and grain products from the high-aluminium category. In addition, cake and 'cake doughnuts' have higher levels of aluminium than bakery products leavened by yeast. Some non-dairy creamers contain aluminium additives while others do not. Furthermore, many manufacturers of salt add aluminium compounds as anticaking agents while others do not. We were unable to obtain the level of detail necessary to distinguish all brands of foods usually consumed. To obtain an accurate assessment of aluminium intake would require a careful inspection of the contents of food packages. It is important to note that the foods analysed by Pennington were collected from grocery stores in three eastern US cities (Lancaster, PA, Nassau–Suffolk, NY, and Rochester, NY) all of which are relatively close to Syracuse and, therefore, the aluminium content of the foods consumed by the study participants are probably similar [8].

Gastrointestinal absorption is highly dependent on the type of aluminium compound as well as the amount [11, 12]. Most aluminium-containing food additives are sulphates, phosphates or silicates [8]. Aluminium phosphate is reported to be insoluble although when consumed in large quantities, urinary excretion of aluminium is elevated [13]. There is little research on the solubility and absorption of aluminium sulphates or silicates in the human body. However, there is considerable evidence that concomitant ingestion of citrate with various aluminium compounds greatly enhances absorption [14–16]. Subjects ingesting aluminium hydroxide with lemon juice have demonstrated elevated serum aluminium concentrations [14]. Dietary acids such as lactic, gluconic, malic, citric and oxalic acids consumed with aluminium in drinking water increased the aluminium concentrations in brain tissue of mice [17]. An epidemiological study of aluminium in drinking water indicated that the

risk of Alzheimer's disease was only elevated when the pH of the water was lower [3].

Tea was one category which did not yield an elevated OR. Dry tea leaves do contain much aluminium [8]. However, when tea is brewed, the concentrations may vary considerably from 0.05 to 1.05 mg per 8-ounce (240 ml) cup [8]. In a case–control study in northern England, the OR for tea consumption (>4 cups/day) was elevated (1.4) but was not statistically significant [18]. French and colleagues indicated that the aluminium, as present in tea, is bound to organic complexes and is poorly absorbed [19]. We did not ascertain whether subjects added lemon juice to their tea in this study. The amount of aluminium present in drinking water in Syracuse is approximately 0.05 mg/l, most of which is present in alumino-hydroxide complexes [20].

Alzheimer's disease is age-dependent, with the incidence rising dramatically with older age [21]. There are changes in the blood–brain barrier with age [22] and aluminium glutamate complex may induce modification of the blood–brain barrier [23]. Aluminium absorption increases substantially in individuals above 76 years of age and absorption is increased in younger Alzheimer patients compared with age-matched controls [16]. Gastrointestinal uptake of aluminium is also elevated in patients with Down's syndrome, which exhibits similar neuropathological features to dementia of the Alzheimer type [24]. Although not all the evidence on aluminium and Alzheimer's disease is consistent [25], there is enough information to suspect that abnormalities of mineral accumulation may be either directly or indirectly associated with this disease. Recently, a clinical trial of desferrioxamine, a chelating agent of aluminium, was shown to slow the rate of decline in performance of daily living skills in patients with Alzheimer's disease [26].

It is time to investigate whether dietary aluminium increases risk in humans and, if so, which factors— such as host characteristics (e.g. age-related differences in gastrointestinal absorption, pre-existing diseases) and diet (e.g. ingestion of acidic foods)—may modify risk. Furthermore, recent evidence of the role of apolipoprotein Eε4 allele in the aetiology of Alzheimer's disease indicates the need to evaluate the presence of this allele with any dietary assessment [27]. There has been an increase in the availability and variety of processed foods containing aluminium additives, as well as considerable interpersonal variation and variation among ethnic groups, in the intake of foods containing such additives. Current dietary patterns in the USA are akin to a grand-scale experiment whereby some individuals are consuming large quantities of aluminium while others are not, the long-term effects of which have not been investigated. It is important to determine whether William Gies was correct in his admonitions.

Key points

- Intake of foods containing aluminium additives is common and can result in the ingestion of amounts far above those obtained from drinking water. Elevated concentrations of aluminium in drinking water have been associated with the development of Alzheimer's disease in some studies.
- The data from this study suggest that individuals who consumed food with a high aluminium content had twice the risk of developing Alzheimer's disease, although the results could be due to random error, since the sample size was small.
- In particular, ingestion of pancakes, waffles, biscuits, muffins, cornbread and/or corn tortillas was associated with an elevated risk of developing Alzheimer's disease.

References

1. McLachlan DRC, Bergeron C, Smith JE, Boomer D, Rifat SL. Risk for neuropathologically confirmed Alzheimer's disease and residual aluminium in municipal drinking water employing weighted residential histories. Neurology 1996; 46: 401–5.

2. Martyn CD, Osmond C, Edwardson JA, Barker DJP, Harris EC, Lacey RF. Geographical relation between Alzheimer's disease and aluminium in drinking water. Lancet 1989; 1: 59–62.

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

4. Flaten TP. Geographical associations between aluminium in drinking water and death rates with dementia, Parkinson's disease and amyotrophic lateral sclerosis in Norway. Trace Elem Med 1987; 4: 179–80.

5. Neri LC, Hewitt D. Aluminium, Alzheimer's disease, and drinking water. Lancet 1991; 338: 390.

6. Forbes WF, McAiney CA. Aluminium and dementia. Lancet 1992; 340: 668–9.

7. Pennington JA, Schoen SA. Estimates of dietary exposure to aluminium. Food Addit Contam 1995; 12: 119–28.

8. Pennington JAT. Aluminium content of foods and diets. Food Addit Contam 1987; 5: 161–232.

9. Gies WJ. Some objections to the use of alum baking-powder. JAMA 1911; 57: 816–21.

10. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. Am J Epidemiol 1986; 124: 453–69.

11. Harris WR, Berthon G, Day JP et al. Speciation of aluminium in biological systems. J Toxicol Environ Health 1996; 48: 543–68.

12. Martin RB. The chemistry of aluminium as related to biology and medicine. Clin Chem 1986; 32: 1797–806.

13. Kaehny WD, Hegg AP, Alfrey AC. Gastrointestinal absorption of aluminium from aluminium-containing antacids. New Engl J Med 1977; 296: 1389–90.

14. Slanina P, Frech W, Ekstrom LG, Loof L, Slorach S, Cedergren A. Dietary citric acid enhances absorption of aluminium in antacids. Clin Chem 1986; 32: 539–41.

15. Walker JA, Sherman RA, Cody RP. The effect of oral bases on enteral aluminium absorption. Arch Intern Med 1990; 150: 2037–9.

16. Taylor GA, Ferrier IN, McLoughlin IJ et al. Gastrointestinal absorption of aluminium in Alzheimer's disease: response to aluminium citrate. Age Ageing 1992; 21: 81–90.

17. Domingo JL, Gomez M, Sanchez DJ, Llobet JM, Corbella J. Effect of various dietary constituents on gastrointestinal absorption of aluminium from drinking water and diet. Res Commun Chem Pathol Pharmacol 1993; 79: 377–80.

18. Forster DP, Newens AJ, Kay DWK, Edwardson JA. Risk factors in clinically diagnosed presenile dementia of the Alzheimer type: a case–control study in northern England. J Epidemiol Commun Health 1995; 49: 253–8.

19. French P, Gardner MJ, Gunn AM. Dietary aluminium and Alzheimer's disease. Food Chem Toxic 1989; 27: 495–6.

20. Driscoll CT, Letterman RD. Chemistry and fate of Al(III) in treated drinking water. J Environ Engineering 1988; 114: 21–37.

21. Hebert LE, Scheer PA, Beckett LA et al. Age-specific incidence of Alzheimer's disease in a community population. JAMA 1995; 273: 1354–9.

22. Mooradian AD. Effect of ageing on the blood–brain barrier. Neurobiol Aging 1988; 9: 31–9.

23. Deloncle R, Guillard O, Huguet F, Clanet F. Modification of the blood–brain barrier through chronic intoxication by aluminium glutamate. Possible role in the aetiology of Alzheimer's disease. Biol Trace Elem Res 1995; 47: 227–33.

24. Moore PB, Edwardson JA, Ferrier IN et al. Gastrointestinal absorption of aluminium is increased in Down's syndrome. Biol Psychiatry 1997; 41: 488–92.

25. Savory J, Exley C, Forbes WF et al. Can the controversy of the role of aluminium in Alzheimer's disease be resolved? What are the suggested approaches to this controversy and the methodological issues to be considered? J Toxicol Environ Health 1996; 48: 615–35.

26. McLachlan DR, Smith WL, Kruck TP. Desferrioxamine and Alzheimer's disease: video home behaviour assessment of clinical course and measures of brain aluminium. Ther Drug Monit 1993; 15: 602–7.

27. Tang MX, Stern Y, Marder K et al. The APOE-ε4 allele and the risk of Alzheimer disease among African Americans, Whites, and Hispanics. JAMA 1998; 279: 751–5.

Harry Hayman, age 100. Veteran of the Somme. © Ian Beesley.