
 Comment

Further thoughts on the aluminum-Alzheimer's disease link

WF Forbes, DRC McLachlan

Abstract

Study objective and method - The results of studies on aluminium (Al) and Alzheimer's disease (AD) from groups in Newcastle, UK and Ontario, Canada were compared in order to explain why the former were unable to detect a link while the latter could, and to suggest alternative ways of examining the data.

Results - The Al concentrations in the Newcastle study were relatively small compared with the Ontario ones. When Al concentrations > 250 µg/l were used, the RRs were greater for AD than for other forms of dementia, and the RRs were lower for those under 75 years and greater at ages 85 years and over than at ages above 75 years. The relationship between dementia and Al concentrations was U or J shaped - there was a minimum at an Al concentration of 100 µg/l. Other constituents or properties such as silicic acid, fluoride, turbidity, iron, and pH all have an effect on the relationship.

Conclusions - Analyses of the type reported from Newcastle can yield further information if they are extended to include multivariate analyses that take account of other water constituents which can affect the relationship between Al water concentrations and AD are carried out. The relationship between Al and dementia may be U or J shaped rather than linear. With regard to AD, the group aged less than 65 years is not the best one in which to explore a relationship. Lastly, it may be that a link with AD is most meaningful at relatively high Al water concentrations.

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topic do not substantiate the conclusions reached in these British papers. Our comments are not intended to challenge the work of the Newcastle group,^{1,2} but to suggest alternative ways of examining data on the link between Al and Alzheimer's disease (AD).

Methods

The water quality data were obtained through the drinking water surveillance programme of the Ontario Ministry of Environment and Energy, as described previously.³ For each locality where a deceased person had resided at his or her time of death, median water quality values were used as a crude estimate of the actual exposure. This procedure is not an accurate measure of exposure since water quality data varied appreciably at different times of the year and in a number of instances over the years. Other uncertainties arise because the water quality data were not available before 1984 and no information was available from death certificates on how long a person had resided in the area where his or her death occurred.

The death certificate data used were for the years 1984-91, for individuals of all ages and for those aged 85 +. Dementia, or more specifically, AD was defined as ICD9 code 331.0. Deaths were counted if these causes were reported as the underlying cause of death. It would have been preferable if AD, recorded on any part of the death certificate, had been used since additional cases of AD would have been ascertained, but this information was not available to us in machine readable form. Moreover, we have no reliable information on the completeness and accuracy of the death certificates as a measure of AD, and none of the recorded AD deaths were verified at post mortem examination. The possibility of errors, because of different certification practices of local doctors, is also indicated because of the relatively large geographical variations in the recording of AD in different parts of Canada. For example, within Canada, the age adjusted mortality rates (for persons aged 65 +) for dementia in the different provinces vary by a factor of about 2. Also, the proportion of deaths ascribed to dementia for those aged 75 + has increased from 0.15% to 3.0%.⁴

Department of Health Studies and Gerontology, University of Waterloo, Waterloo, Ontario, N2L 3G1, Canada
W F Forbes

Center for Research in Neurodegenerative Diseases, University of Toronto, Ontario, Canada
D R C McLachlan

Correspondence to:
Dr W F Forbes

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In two recent papers in this journal,^{1,2} the issue of the aluminum-Alzheimer's disease link was discussed and on the basis of results obtained, the authors were unable to detect a large effect epidemiologically in the onset of Alzheimer's type of dementia when examining exposure to aluminum (Al). These studies appear to have been carried out carefully, and the conclusions based on the results seem justified. However, results from some Canadian studies on this

Table 1 The relationship between selected water quality variables and the reporting of Alzheimer's disease (ICD 9=331.0) on death certificates for individuals aged 85 and over*

Water quality variable	Rate ratios						
Al ($\mu\text{g/l}$):							
≤ 67	(1.00)	(1.00)	(1.00)	(1.00)	(1.00)	(1.00)	(1.00)
68-250	0.85†	0.88	0.91	0.89	0.91	0.90	0.89
> 250	4.76†	4.93†	5.07†	6.27†	7.38†	7.56†	9.95†
Source:							
Ground		(1.00)	(1.00)	(1.00)	(1.00)	(1.00)	(1.00)
Surface		0.91	0.76	0.82	0.77	0.76	0.88
Silicic acid (mg/l):							
< 1.5			(1.00)	(1.00)	(1.00)	(1.00)	(1.00)
≥ 1.5			0.81†	1.01	0.96	1.03	1.10
Iron (mg/l):							
< 6.2				(1.00)	(1.00)	(1.00)	(1.00)
6.2-18.0				0.72†	0.75†	0.84	0.95
> 18.0				0.71†	0.64†	0.76	0.94
pH:							
< 7.85					(1.00)	(1.00)	(1.00)
7.85-7.95					0.58†	0.50†	0.48†
> 7.95					0.82	0.78	0.52†
Fluoride (mg/l):							
< 0.5						(1.00)	(1.00)
0.5-0.98						0.83	0.71†
> 0.98						1.23†	1.20
Turbidity (formazin units):							
< 33							(1.00)
> 33							0.58†

* n=1041; † p < 0.05.

The data on the autopsy verified AD were obtained as described previously.⁵

The results estimating the relative risk shown in table 1 are based on the rate ratios (derived from Poisson regressions) for particular categories. The rates from which the rate ratios were obtained are the proportions of death certificates reporting dementia for particular groups. A rate ratio is calculated relative to the selected reference category, which necessarily has a rate ratio of 1.00 (shown in parenthesis). With respect to the results shown in table 1, it should be noted that the rate ratios depend on the cut off levels selected. These results represent the results of one out of over 100 analyses, using different cut off levels.

Results and discussion

The tentative nature of any inferences drawn from observed associations between exposure to environmental Al and the incidence of AD must be stressed. This arises because of the following:

- People frequently move from place to place,
- The lag period between the neurotoxic effects of an environmental agent and the onset of AD is not known,
- There are uncertainties about the diagnosis of AD, perhaps particularly at the higher ages, and,
- Complex interactions would be expected to occur between the genetically determined causal factors, neuroprotective factors, neurodegenerative changes associated with aging, and the competing effects of other brain diseases.

These topics are not well understood but it is likely that they affect the putative link between Al and AD. Moreover, these studies do not consider sources of exposure to Al from sources other than drinking water. This latter concern applies to all studies investigating this association. At the same time, the associations between Al water concentrations and AD

should be explained. There are a number of issues as we describe below.

Firstly, the Al concentrations on which the Newcastle results are based are relatively small, or at least smaller than many Al water concentrations in Canada. More specifically, among the data points given in figure 1 of the second paper,² there are only four points for which the Al water concentrations are above 100 $\mu\text{g/l}$ and no points for which Al water concentrations are above 125 $\mu\text{g/l}$. In Ontario, on the other hand, there are a number of areas where the Al water concentrations exceed 250 $\mu\text{g/l}$. It is at these higher concentrations where the estimated relative risks between the Al water concentrations and indications of AD are most pronounced (see table 1, comparing the prevalence of AD in areas where the Al water concentrations are relatively high, compared with areas where they are relatively low).

Secondly, when the Al water concentrations above 250 $\mu\text{g/l}$ are used, (see table 1) the relative risks are greater for AD than for other forms of dementia, and the relative risks are lower for individuals below the age of 75³ and greater at ages above 85 than at the ages above 75 (see table 1 and ref 3). This suggests that the effects of Al become more important at the higher ages, possibly because the greater cumulative exposure over the lifetime or because of a greater susceptibility to the effects of Al at the higher ages. Moreover, this risk estimate may still be underestimated because of the previously mentioned likelihood that AD, although present, was not recorded as the underlying cause of death on the death certificate and because of the unavailability of some water quality data, particularly for early exposure.

Thirdly, there is evidence that the relation between dementia and Al water concentrations is U shaped or J shaped - that is, that there is a minimum at about 100 $\mu\text{g/l}$. This type of relation has been observed for the above mentioned death certificate data, and also for the association based on results of a mental status questionnaire.⁶ It may be noted that the results in the Newcastle papers,^{1,2} although not statistically significant, are consistent with a J or U shaped relationship - that is, a minimum tends to be observed at Al water concentrations between 50 and 150 $\mu\text{g/l}$ (see table 3 of ref 1). In other words, a non-linear relationship may account for the results obtained in England^{1,2} and by other workers in the area where the Al water concentrations are relatively low.⁷ An example of this is provided by a Swiss study⁸ in which the 'exposed' population resided in areas where the Al water concentrations were about 100 $\mu\text{g/l}$.

Fourthly, in examining the relationship between Al water concentrations and various indications of dementia, and particularly AD, it is better to examine more than the bivariate relationships, since a number of studies have indicated that other water constituents or properties such as silicic acid, fluoride, turbidity, iron, and pH have an appreciable effect on the relationship. We provide an example in table 1. The relative risks for relatively high Al

water concentrations and the presence of AD listed as the underlying cause of death on death certificates is about 5 when only Al water concentrations are considered. However, when other water constituents are taken into account, the relative risk estimates attain a value of nearly 10. The data shown in table 1, incidentally, also show the J or U shaped relationship mentioned earlier. More specifically, for the different Al concentrations, a minimum is observed in the concentration range 68 to 250 µg/l, and above 250 µg/l a relative risk estimate of 9.95 is obtained. A statistically significant lower relative risk is also observed for fluoride concentrations between 0.5 and 0.98mg/l and for a relatively greater turbidity (which presumably also contains aluminium). Consistent with previous results,³ a lower risk is associated if the pH is between 7.85 and 7.95.

Table 1 shows one set of analyses and other results are obtained if different cut off levels are used. The choice of cut off levels affect the significance levels, which also depend on the water constituents that are included in the multivariate analyses. For example, under certain circumstances silicic acid and iron concentrations afford statistically significant associations. At the same time, statistically significant associations are consistently obtained for aluminium concentrations above 250 µg/l.

In summary, we suggest that analyses of the type reported at Newcastle can yield additional information if the appropriate multivariate analyses which take into account other water constituents are carried out. We make this suggestion since these other constituents can affect the relation between Al water concentra-

tions and AD. In addition, it is perhaps inappropriate to assume a linear relationship between Al water constituents and indications of dementia. This is because there may be a J or U shaped relationship between Al water concentrations and AD; and if the interest is mainly in AD, the age group below the age of 65 is not the best group in which to investigate the relevant associations. Moreover, it may be that only at relatively high Al water concentrations is the link with AD most meaningful, and it should be noted that some studies, such as the Newcastle one, were carried out in areas with relatively low Al water concentrations.

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