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GEOGRAPHICAL RELATION BETWEEN ALZHEIMER'S DISEASE AND ALUMINIUM IN DRINKING WATER

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Summary In a survey of eighty-eight county districts within England and Wales, rates of Alzheimer's disease in people under the age of 70 years were estimated from the records of the computerised tomographic (CT) scanning units that served these districts. Rates were adjusted to compensate for differences in distance from the nearest CT scanning unit and for differences in the size of the population served by the units. Aluminium concentrations in water over the past 10 years were obtained from water authorities and water companies. The risk of Alzheimer's disease was 1·5 times higher in districts where the mean aluminium concentration exceeded 0·11 mg/l than in districts where concentrations were less than 0·01 mg/l. There was no evidence of a relation between other causes of dementia, or epilepsy, and aluminium concentrations in water.

Introduction

ALUMINIUM has been detected in both senile plaques[1] and neurofibrillary tangle bearing neurons[2] in brains of patients with Alzheimer's disease. These findings suggest that exposure to aluminium may be important in causation of the disease. Aluminium is ubiquitous in the environment and in Britain some 5–10 mg is ingested each day.[3] However, only a very small proportion of this ingested aluminium is absorbed.[4]

In many parts of Britain aluminium sulphate is used as a coagulant in the treatment of water. Its purpose is to help with the removal of suspended matter and highly coloured humic substances, thus reducing the dose of chlorine later required to ensure satisfactory microbiological quality. Most of the aluminium added is also removed in the process of clarification but residual amounts may pass into supply. Water treatment plants should be operated so as to keep the residual concentration as low as possible. For aesthetic reasons the current European Community directive specifies a maximum acceptable concentration of 0·2 mg/l. Aluminium from drinking water forms only a small part of the total daily intake but because the aluminium is largely uncomplexed it may make a disproportionate contribution to the total amount absorbed from the gastrointestinal tract.

To examine the possible relation between exposure to aluminium in water and the development of Alzheimer's disease we conducted a survey in eighty-eight county districts within England and Wales with differing concentrations of aluminium in the water supply. The incidence of Alzheimer's disease in each district was estimated from diagnostic rates in people aged under 70 years. Diagnostic rates were obtained by examining records of computerised tomographic (CT) scanning centres. Mean concentrations of aluminium in water in each district over the previous 10 years were calculated from information supplied by water undertakings.

Methods

The county districts studied were within Northumberland, Durham, and Tyne and Wear; Lancashire, Merseyside, Cheshire, and Clwyd; Nottinghamshire and Derbyshire; Norfolk, Suffolk, and Cambridgeshire; Dyfed, West Glamorgan, Mid Glamorgan and South Glamorgan, and Gwent; Devon and Cornwall; and Hampshire and the Isle of Wight. These places were chosen to represent a wide range of water aluminium concentrations within different parts of the country. Although there were exceptions, the concentrations of aluminium in water in the chosen county districts within each area tended to be similar. The highest concentrations were found in Northumberland, Tyne and Wear, and Durham, and in Devon and Cornwall; the lowest in Norfolk, Suffolk, and Cambridgeshire, in Nottinghamshire and Derbyshire, and in Hampshire.

Measurements of Rates of Alzheimer's disease

Cases of dementia were ascertained from the records of CT scanning units. Two of us (C. N. M., E. C. H.) visited units within the seven study areas and examined their records to identify all patients aged 40–69 years scanned because of the presence of clinical features of a dementing illness. Where possible, records of all scans conducted over a 3-year period, either 1983–85 or 1984–86 were examined. For 4 of the units this was not practicable either because the CT scanner had not been in operation for 3 years or because adequate records were not available; records for a shorter period were then used.

Patients with dementia were classified into four categories according to the clinical information supplied on a request form and the radiologist's report of the CT scan. Criteria for inclusion in each category are given below:

Probable Alzheimer's disease.—The clinical information supplied on the request form specified Alzheimer's disease or dementia or contained at least two of the following clinical features: deterioration of memory, intellectual deterioration, persistent confusion, dysphasia in the absence of hemiparesis. There was no history of stroke, systemic hypertension, alcohol abuse, or epilepsy, nor was there any other indication of any specific cause for dementia. The CT scan was reported either as normal or as showing only cerebral atrophy.

Possible Alzheimer's disease.—The clinical information supplied indicated a history of intellectual deterioration but without additional details. The CT scan was reported either as normal or as showing only cerebral atrophy.

Cerebrovascular dementia.—The clinical information indicated a history of stroke, transient ischaemic attacks, or recent epilepsy as well as features of a dementing illness, or the CT scan was reported as showing evidence of cerebral infarction including lacunar infarction or Binswanger's syndrome.

Dementia from other causes.—Patients were placed in this category when either the clinical information on the request form or the report of the CT scan provided evidence of a specific cause for the dementing illness. The commonest diagnoses in this group were Huntington's disease, multiple head injury, and chronic alcohol abuse.

A study of 52 consecutive cases of presenile dementia scanned at the Wessex Neurological Centre, Southampton General Hospital, showed that classification of the type of dementia from the clinical information supplied on the request form for the CT scan and from the radiologist's report was in good agreement with the final clinical diagnosis recorded in the patients' case-notes. Of 24 cases classified as probable Alzheimer's disease 19 had Alzheimer's disease recorded as the final clinical diagnosis.

To examine the effect of differences in referral practices between areas we also identified patients within the same age range who were investigated by CT scanning because of epilepsy.

Rates of disease for each diagnosis in each county district were directly age-standardised to the 40–69-year-old population of England and Wales for 1983 by 5-year bands. Analysis was restricted to eighty-eight county districts served exclusively by CT scanning centres within the seven areas.

Estimation of Water Aluminium Concentrations

From the water undertakings responsible for supplying the eighty-eight county districts we obtained details concerning type of source, water treatment processes in use, and distribution of supply for all water sources contributing more than 5% of the total supply. We also obtained data about residual aluminium concentrations for each water source over the previous 10 years. Analytical methods for measuring aluminium in water have changed over the past 10 years and different water undertakings may have used different methods at different times. Estimates of mean water aluminium concentrations were therefore divided into five groups. The first group contained county districts with concentrations of 0·01 mg/l or less. None of these districts had used aluminium coagulation in water treatment during the previous decade and aluminium in their waters was usually undetectable. The other four groups, in which aluminium concentrations ranged from 0·02 to 0·20 mg/l, were divided so that they contained approximately equal numbers of people at risk.

The relation between age standardised rates of Alzheimer's disease, other categories of dementia and epilepsy, and mean concentration of aluminium in water was investigated by use of log linear and logistic regression analysis.

Results

We identified 1203 patients with one of the four categories of dementia. 18 had to be excluded because details of their age or place of residence could not be found. 445 of these patients (37%) were classified as having probable Alzheimer's disease. Table I gives the numbers of patients in each of the diagnostic categories. There were 2997 patients with epilepsy, of whom 61 had to be excluded because of inadequate information.

In calculating the rates for dementia and epilepsy it was necessary to take account of the effects of distance of the county district from the nearest CT scanning centre. Table II shows that rates for all diagnostic categories of disease were lower in county districts only a few miles from the scanner than those for the districts in which the scanner was located. Further increase in distance had little effect on rates.

Because the size of the population served by an individual CT scanning unit varied between areas, we examined how the total annual number of brain scans performed per 1000 population influenced our estimates of rates of disease. Scanning rates varied threefold between different areas but the corresponding variation in rates of dementia and epilepsy was less than 1·4.

The relation between aluminium and rates of disease in the different diagnostic categories is summarised in table III. Rates have been adjusted to take account of distance of county districts from the nearest CT scanning centre and differences in scanning rates between centres. Rates of disease in districts where concentrations of aluminium in water were less than 0·01 mg/l were 5·4 per 100 000 for probable Alzheimer's disease, 3·0 per 100 000 for possible Alzheimer's disease, and 6·3 per 100 000 for dementia from other causes. The rate for all causes of dementia combined was 14·7 per 100 000 and for epilepsy it was 37·6 per 100 000. These rates have been taken as a baseline and rates of disease in the other four groups of districts with increasing water aluminium concentrations have been expressed as a risk relative to this baseline.

The risk for all causes of dementia combined exceeded unity in all groups of districts where concentrations of

TABLE I—NUMBERS OF DEMENTED PATIENTS

Diagnostic category	Men	Women
Probable Alzheimer's disease	242	203
Possible Alzheimer's disease	112	109
Cerebrovascular dementia	162	111
Other causes of dementia	154	92

TABLE II—EFFECT OF DISTANCE FROM COUNTY DISTRICT OF RESIDENCE TO CT SCANNING UNIT ON DIAGNOSTIC RATES OF DISEASE (PER 100 000 POPULATION)

Distance from CT scanning unit (miles)	Probable Alzheimer's disease	Possible Alzheimer's disease	Other causes of dementia	Epilepsy
0 (county district containing scanner)	7·5	4·0	9·4	46 4
6–10	3 7	1·8	4·6	29·5
11–15	4 7	2·1	4·7	26·7
16–25	3·7	1·7	3·4	24·7
>26	4·0	1·9	5·2	25·6

TABLE III—RELATIVE RISKS (95% CI) OF ALZHEIMER'S DISEASE, DEMENTIA FROM OTHER CAUSES, AND EPILEPSY IN PATIENTS AGED 40–69 IN COUNTY DISTRICTS GROUPED ACCORDING TO WATER ALUMINIUM CONCENTRATION (RISKS ADJUSTED FOR DISTANCE FROM CT SCANNING UNIT AND CT SCANNING RATE)

Aluminium concentration (mg/l)	Probable Alzheimer's disease n=445	Possible Alzheimer's disease n=221	Other causes of dementia n=519	Epilepsy n=2920
0-0·01	1	1	1	1
0·02-0·04	1·5 (1·0–2·2)	1·1 (0·7–1·8)	1·2 (0·9–1·7)	0·9 (0·8–1·1)
0·05-0·07	1·4 (1·0–1·9)	1·1 (0·7–1·7)	1·1 (0·8–1·4)	0·9 (0·8–1·0)
0·08-0·11	1·3 (0·9–2·0)	0·8 (0·5–1·4)	1·0 (0·7–1·4)	0·9 (0·8–1·1)
>0·11	1·5 (1·1–2·2)	1·2 (0·7–1·9)	1·2 (0·8–1·6)	0·9 (0·8–1·1)

aluminium were greater than 0·01 mg/l. Separate examination of the different diagnostic categories of dementia showed that the increase in risk was restricted to one diagnostic category—probable Alzheimer's disease. In this category, relative risks for groups of districts where aluminium concentrations exceeded 0·01 mg/l ranged from 1·3 to 1·5 (see table III). After exclusion of patients aged 65 years or older, the relative risk in the highest aluminium group reached 1·7 (95% confidence interval 1·1–2·7) and a gradient of risk was present with increasing concentrations of aluminium (table IV). A relation between aluminium and probable Alzheimer's disease was also present when sexes were examined separately although the effect did not reach the 5% level of statistical significance for women.

Relative risks for possible Alzheimer's disease, cerebrovascular dementia, and other causes of dementia tended to be slightly greater than unity in districts where water aluminium concentrations were greater than 0·01 mg/l but the relative risk never exceeded 1·2 and none was statistically significant. In the tables, the diagnostic categories cerebrovascular dementia and other causes of dementia are shown combined.

No relation between water aluminium concentrations and epilepsy was found. Relative risks were either 1 or 0·9 in all ranges of aluminium concentrations.

TABLE IV—RELATIVE RISKS (95% CI) OF ALZHEIMER'DISEASE, DEMENTIA FROM OTHER CAUSES, AND EPILEPSY IN PATIENTS AGED 40–64 (RISKS ADJUSTED FOR DISTANCE FROM CT SCANNING UNIT AND CT SCANNING RATE)

Aluminium concentration (mg/l)	Probable Alzheimer's disease n=307	Possible Alzheimer's disease n=153	Other causes of dementia n=372	Epilepsy n=2461
0-0·01	1	1	1	1
0·02-0·04	1·4 (1·0–2·2)	0·9 (0·5–1·5)	1·2 (0·8–1·7)	1·0 (0·8–1·1)
0·05-0·07	1·4 (1·0–2·2)	1·1 (0·7–1·8)	1·1 (0·8–1·6)	0·9 (0·8–1·1)
0·08-0·11	1·6 (1·0–2·5)	0·6 (0·3–1·2)	1·2 (0·8–1·8)	1·0 (0·9–1·2)
>0·11	1·7 (1·1–2·7)	0·9 (0·5–1·6)	1·2 (0·8–1·8)	1·0 (0·8–1·1)

TABLE V—RELATIVE RISKS (95% CI) OF ALZHEIMER'S DISEASE AND DEMENTIA FROM OTHER CAUSES ESTIMATED FROM PROPORTIONAL RATES IN PATIENTS AGED 40–69 IN COUNTY DISTRICTS GROUPED ACCORDING TO WATER ALUMINIUM CONCENTRATIONS

Aluminium concentration (mg/l)	Probable Alzheimer's disease n=445	Possible Alzheimer's disease n=221	Other causes of dementia n=519
0-0·01	1	1	1
0·02-0·04	1·5 (1·1–2·1)	1·0 (0·6–1·5)	1·1 (0·9–1·6)
0·05-0·07	1·5 (1·1–2·1)	1·0 (0·7–1·6)	1·1 (0·8–1·5)
0·08-0·11	1·4 (0·9–2·1)	0·8 (0·6–1·7)	1·0 (0·7–1·4)
>0·11	1·6 (1·1–2·4)	1·0 (0·6–1·6)	1·1 (0·8–1·5)

As another method of examining the effect on diagnostic rates of distance from the CT scanner and the size of the population served by a CT scanner, we related numbers of cases in each category of dementia to the total number of cases of epilepsy and dementia for each district. In this way we hoped to take account of differences between areas in their practices of referral and CT scanning. Logistic regression analysis revealed that this ratio varied little with changes in distance from the scanner or with population size. The relation between water aluminium concentrations and probable Alzheimer's disease was still present. These results are summarised in table V.

Discussion

This survey, conducted in eighty-eight county districts within England and Wales, shows that rates of Alzheimer's disease in people under the age of 70 years are related to the average aluminium concentrations present in drinking water supplies over the previous decade. The relation to water aluminium concentrations was specific to the group of patients in whom the diagnosis of Alzheimer's disease was most certain; no such relation with any of the other diagnostic categories of dementia or to epilepsy was present.

We used diagnostic rates of dementia in patients under the age of 70 years to estimate the incidence of Alzheimer's disease because we judged that most patients in this age group who presented with symptoms of cognitive impairment would be referred to neurologists, psychiatrists, and other hospital specialists with expertise in dementia and that their subsequent investigation would include a CT brain scan. Younger patients with dementia are generally investigated more aggressively and case ascertainment is likely to be more complete. In the analysis we examined separately a subgroup of patients under the age of 65 years and found a closer relation between aluminium concentrations and Alzheimer's disease than in patients under the age of 70 years.

Apart from age, there are several factors that may affect whether patients with dementia receive a CT brain scan and hence influence our estimates of disease rates. Where differences in diagnostic rates were in part dependent upon differences in the size of the population served by the CT scanner or the distance of a county district from the nearest CT scanning centre, it was possible to make adjustment during the analysis. As an alternative method of controlling for these and other possible influences on the diagnostic rate of dementia we took another diagnosis, epilepsy, and analysed the rate of dementia as a proportion of the rates of dementia and epilepsy combined. In this analysis no adjustment for the effect of either distance of the county district from the CT scanning unit or the local CT scanning rate was necessary. A positive relation between rates of Alzheimer's disease and water aluminium concentrations was present whichever way the data were analysed. Neither method of analysis suggested a relation between water aluminium and other categories of dementia. We conclude that the relation is not likely to be a result of variation in referral patterns or scanning practices between areas.

The current view of Alzheimer's disease is that neuropathological confirmation is required for definite diagnosis.[5] However, several studies have demonstrated that in about 80% of cases a diagnosis made on clinical features alone is in accord with the neuropathological findings[6,7] and that CT scanning is helpful in the differential diagnosis of dementia.[8] Our categorisation of dementia, based only on

information from the CT scan request form and the CT scan report, conformed closely to the clinical diagnosis. The majority of patients in our diagnostic category of probable Alzheimer's disease could be expected to show neuropathological features of Alzheimer's disease. We should point out that the likely effect of misclassification of type of dementia and incompleteness of case ascertainment would be to obscure any relation between aluminium concentrations and Alzheimer's disease and to reduce the magnitude of the estimate of relative risk.

Although detailed information about the concentrations of aluminium in the water supply to individual county districts did not become available until identification and categorisation of patients had been completed, the investigators collecting data from CT scanning units were aware, in broad terms, of the aluminium concentrations present in each area. This could have produced a bias in the allocation of patients to different disease categories. However, criteria for inclusion in each category were strictly defined at the beginning of the study and a relation with aluminium is still present when all categories of dementia are combined, or when the categories of probable and possible Alzheimer's disease are analysed together. Bias in the classification of dementia is unlikely to explain our results.

Because aluminium in drinking water makes only a small contribution to the total intake of aluminium a relation between concentrations of aluminium in water and Alzheimer's disease is, at first sight, surprising. However, urinary excretion of aluminium is only 0·02 to 0·05 mg per day.[4] This represents less than 1% of the 5–10 mg ingested daily, so most dietary sources of aluminium are presumably not absorbed. Aluminium in drinking water is either dissolved or readily brought into solution and its bioavailability may therefore be much higher than aluminium from other sources. Moreover, if other sources of dietary aluminium also contribute to Alzheimer's disease, this will tend to diminish the strength of any relation with aluminium in drinking water.

Epidemiological evidence from Norway has previously suggested a link between the concentration of aluminium in water and dementia.[9,10] In these studies there was no attempt to distinguish between different causes of dementia and the use of mortality data has also been criticised.[11] Mortality data for dementia have been shown to contain serious biases in England and Wales[12] and in Australia.[13] Although Norwegian data may be more reliable, the relevance of these studies to Alzheimer's disease is hard to assess in the absence of evidence that mortality from dementia reflects the incidence of Alzheimer's disease.

The results of the present survey provide evidence of a causal relation between aluminium and Alzheimer's disease. However, care is needed in interpretation because, as in all epidemiological surveys, the possibility exists that the relation observed is due to the operation of some unknown confounding variable. Further studies in different populations are required to confirm these results and we are now conducting a case-control study to investigate the relation between dietary aluminium and Alzheimer's disease at an individual level.

This work would not have been possible without the willing cooperation of the water authorities and water companies supplying the areas in the survey. We are most grateful to them for their assistance. We are also indebted to Dr A. Appleby, Dr L. Brock, Dr E. H. Burrows, Dr A. Carty, Dr P. Cook, Dr K. Grant, Dr T. D. Hawkins, Dr I Holland, Dr M. Hourihan, Dr V. McAllister, Dr P. Norman, Dr R. Paxton, Dr J. Pilling, Dr R. Sellwood, and Dr E. Wyn Jones for letting us examine the records of their CT scanning units.

References at foot of next column

COLD-INDUCED PULMONARY OEDEMA IN SCUBA DIVERS AND SWIMMERS AND SUBSEQUENT DEVELOPMENT OF HYPERTENSION

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Summary The effect of cold and/or a raised partial pressure of oxygen was examined in eleven people with no demonstrable cardiac abnormality but who had pulmonary oedema when scuba diving or surface swimming, and in ten normal divers. These stimuli induced pathological vasoconstriction in the pulmonary oedema group, nine of whom also showed signs of cardiac decompensation when so stimulated. The pulmonary oedema patients have been followed-up for an average of 8 years. Seven have become hypertensive. Except for the onset of lone atrial fibrillation in one normotensive female diver and development of Raynaud's phenomenon in a normotensive man, there have been no cardiovascular events and no deaths.

Introduction

ACUTE pulmonary oedema occurs when the pulmonary capillary permeability is increased (non-cardiogenic pulmonary oedema) or when the pulmonary capillary hydrostatic pressure exceeds the plasma oncotic pressure (cardiogenic pulmonary oedema). The term cardiogenic pulmonary oedema implies that the primary defect causing the oedema is within the left heart. Although this may be the case in such conditions as myocardial infarction, there is

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