Aluminium toxicity during regular haemodialysis

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Summary and conclusions

In the west of Scotland the incidence of dialysis encephalopathy has been confined to three geographical areas where the concentration of aluminium in the water supply is greatly increased owing to the addition of aluminium sulphate. Eight patients with encephalopathy who dialysed at home in these areas had greatly increased serum aluminium concentrations, and a significant correlation was found between serum aluminium concentrations and the concentrations of aluminium in the water supply.

This study provides further evidence that the dialysis encephalopathy syndrome is due to aluminium intoxication, the major source of aluminium being the water supply from which dialysis fluid is prepared.

Introduction

Evidence is accumulating to suggest that the dialysis encephalopathy syndrome is due to aluminium intoxication,[1 2] arising primarily from aluminium contamination of the domestic water supply.[3 4] In the west of Scotland the incidence of dialysis encephalopathy has been confined to three regions where the aluminium concentration of the water supply is relatively high; no case has occurred in Glasgow, where aluminium concentrations in water are negligible.

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We analysed the concentrations of aluminium and other elements in domestic water supplies in the west of Scotland dialysis area, and measured serum aluminium concentrations in patients receiving dialysis in this area.

Patients and methods

Samples of tap water (from which dialysis fluid is prepared) were collected from the homes of all patients receiving maintenance haemodialysis, from the homes of patients who had died of dialysis encephalopathy, and from the renal units of Stobhill General Hospital and the Royal Infirmary, Glasgow. Blood samples were obtained from all patients receiving dialysis, including five patients with dialysis encephalopathy. Stored serum samples from three further patients who had died of encephalopathy were also available. Control samples were obtained from 20 subjects with normal renal function and from 15 patients with chronic renal failure (mean serum creatinine concentration 1008 μmol/l (11·4 mg/100 ml)) who did not then need dialysis.

The diagnosis of dialysis encephalopathy was based on typical clinical features at presentation and electroencephalographic findings,[5] and other possible causes were excluded by full investigation. There were no significant differences between the groups of dialysis patients in duration of maintenance dialysis treatment, dialysis treatment schedules, equipment, or medication. All but four patients took aluminium hydroxide regularly as a phosphate-binding agent.

Analyses—All water samples were analysed by the water department of Strathclyde regional council using a colorimetric technique, and data were provided on aluminium, iron, manganese, copper, zinc, calcium, magnesium, and silicon concentrations. The water department records of routine analysis were consulted to confirm that the results for individual samples were representative of a particular supply. Serum samples were analysed for aluminium by atomic absorption spectrophotometry using electrothermal atomisation. (Full details of this method will be published elsewhere and are available on request.)

Results

Since 1972, 13 cases of the dialysis encephalopathy syndrome have occurred (see table). The mean (±SE) aluminium concentration of the domestic water supplies of these 13 patients was 14·8±1·2 μmol/l (400±33·3 μg/l), which was significantly higher ($P < 0·001$; Mann-Whitney U test) than the mean concentration of <1·1 μmol/l (<30 μg/l) found in the water supplies of 40 patients who dialysed in the

Clinical details of patients with dialysis encephalopathy

Case No	Sex	Age when dialysis begun (years)	Months on dialysis before symptoms developed		Bone disease	Survival (months)	Clinical features at or before death
			Home	Hospital			
1	M	29	30	8*		3	Sudden death
2	M	43	38	4*	Osteomalacia (minimal)	3	Progressive neurological deterioration
3	M	44	28	4	Osteomalacia (minimal)	1	Sudden death
4	M	28	27	6		2	Sudden death
5	M	43	20	2		5	Progressive neurological deterioration
6	M	38	24	24*		2	Progressive neurological deterioration
7	M	30	24	48	Hyperparathyroidism	5	Progressive neurological deterioration
8	M	33	44	5	Hyperparathyroidism and osteomalacia	4	Progressive neurological deterioration
9	F	21	24	6	Osteomalacia	4	Progressive neurological deterioration
10	M	28	36	8*	Osteomalacia	>5	Disabled
11	F	50	14	5	Osteomalacia	>3	Disabled
12	M	34	4	4		1	Sudden death
13	M	20	37	14*		>2	Well

*Renal transplantation.

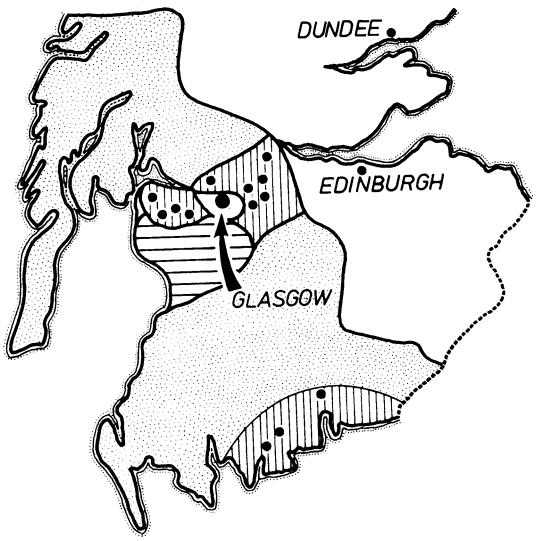

FIG 1—Regions in west of Scotland dialysis area with moderately high (horizontal bars) and very high (vertical bars) concentrations of aluminium in water supply. ●= Homes of patients with dialysis encephalopathy.

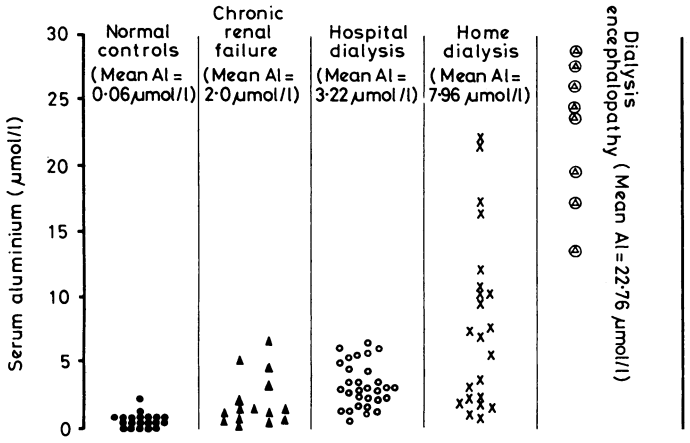

FIG 2—Serum aluminium (Al) concentrations in 20 normal controls, 15 patients with chronic renal failure, 30 and 22 patients receiving hospital and home dialysis respectively, and eight patients with dialysis encephalopathy.
Conversion: SI to traditional units—Aluminium: 1 μmol/l ≈ 27 μg/l.

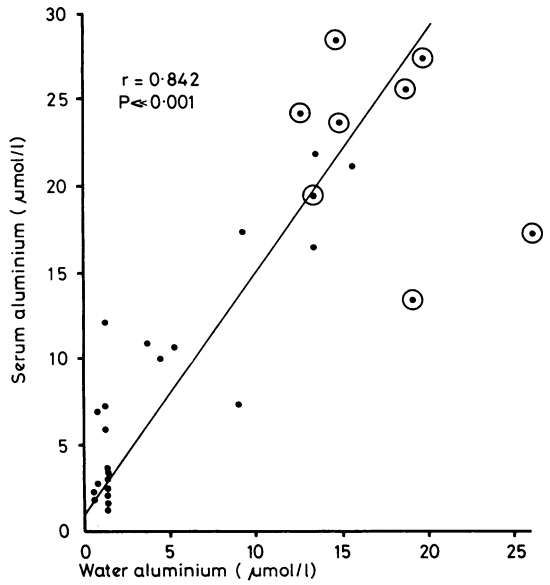

FIG 3—Correlation between water aluminium and serum aluminium concentrations in 22 patients receiving home dialysis and eight patients with dialysis encephalopathy (encircled).

Glasgow area, where no case of encephalopathy has occurred. No consistent difference was found in concentrations of the other elements measured, and we could not confirm the suggestion that manganese, calcium, or fluoride might also be implicated.[4]

Figure 1 shows the distribution of cases of encephalopathy in the west of Scotland dialysis area and the concentrations of aluminium in the water supply to the different areas. Comparison of the serum aluminium concentrations in the different populations studied (fig 2) showed that the highest values occurred in patients with dialysis encephalopathy, high values also being found in four patients who dialysed in suspect areas. Figure 3 shows a significant linear relation between concentrations of aluminium in serum and water.

Discussion

Our results provide further evidence to suggest that aluminium intoxication is the cause of the dialysis encephalopathy syndrome. The 13 patients with encephalopathy received home dialysis in three areas with a high aluminium content in the water supply. This is consistent with the observed geographical distribution; none of the 40 patients who dialysed in Glasgow, where the aluminium content of the water supply is negligible, developed encephalopathy. Alum (aluminium sulphate) is used as a coagulant to remove organic material from water and improve its clarity. Alum is added to most water supplies in the west of Scotland, with the exception of Glasgow, and it is the undoubted source of the high aluminium content in the water of the suspect areas.

All patients with greatly increased serum aluminium concentrations received home dialysis in areas with a high aluminium content in the water supply. The highest values were found in the eight patients with encephalopathy, from whom blood samples had been obtained at the onset of symptoms, and in four other patients who dialysed in suspect areas. These four patients did not have dialysis encephalopathy, but three of the four had symptoms or signs which we now think are premonitory features of dialysis encephalopathy—namely, general malaise, vomiting, weight loss, fall in haemoglobin concentration, and muscular or bony pains. The fourth patient received a cadaveric renal transplant shortly after his serum aluminium concentration was measured.

We observed an increased incidence of severe renal osteomalacic disease in our encephalopathic group. Four of the 13 patients (31%) developed symptoms and radiological appearances typical of osteomalacia, as compared with an incidence of about 10% in the rest of our home dialysis population. This confirms the findings of other studies[3,6] in which a more definite relation between bone disease, encephalopathy, and water supply is reported. We also observed that haemoglobin values in the encephalopathic patients fell during the year before neurological symptoms developed. A fall in haemoglobin was also seen in three of the four other patients with very high serum aluminium concentrations, and we have some preliminary evidence that aluminium may be toxic to the enzymes concerned in haem biosynthesis.[7]

Our findings suggest that aluminium retention occurs in all patients with renal impairment. The ingestion of aluminium hydroxide may be a contributory factor, but the major source is the high aluminium content of the water supply from which dialysis fluid is prepared. The highest serum aluminium concentrations occurred acutely when patients were exposed to very high aluminium concentrations in water, and in our two most recent cases of dialysis encephalopathy the syndrome developed rapidly after the water aluminium content had exceeded 37 μmol/l (1000 μg/l). When patients are removed from further exposure to aluminium the serum aluminium concentration gradually falls, presumably as a result of aluminium deposition in bones and other tissues. At this stage the clinical state may improve, but further aluminium accumulation eventually gives rise to recurrence of the syndrome and to irreversible intoxication or damage unless the patient can be permanently removed from exposure to aluminium by means

of successful transplantation[8] or by dialysis using a water purification system.

We conclude that aluminium contamination of the water used for dialysis is the probable cause of dialysis encephalopathy. The resulting aluminium intoxication is not confined to the nervous system but is almost certainly a factor in causing bone disease and possibly also in aggravating anaemia. We reiterate the advice of others[4] that all patients who dialyse in areas with a high concentration of aluminium in the water should use some form of water purification system, though this will not necessarily protect patients who have already accumulated large amounts of aluminium. At present the use of deionisers or reverse-osmosis apparatus may be the most effective method of extracting aluminium from the water, but more-specific techniques may be devised if it can be confirmed that aluminium is the only potential toxin in the supply to an area.

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Serum ionised calcium concentration: measurement versus calculation

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Summary and conclusions

Four hundred and eighteen measurements of serum ionised calcium, total calcium, and protein concentrations were made from 47 normal volunteers, 104 patients with chronic renal failure (33 being treated conservatively and 71 with regular haemodialysis), and 83 renal transplant recipients. The serum ionised calcium concentration was measured with an Orion SS-20 meter and calculated from the total serum calcium and protein concentrations by using three formulae and a nomogram. In the normal subjects and patients undergoing regular haemodialysis, whose serum calcium concentrations were in or near the normal range, three of the calculations gave results similar to those obtained by direct measurement. In patients with conservatively treated chronic renal failure and those who had received renal transplants, however, there was poor agreement between the methods. When patients with hypercalcaemia and hypocalcaemia from all the groups were considered separately there was again poor agreement between calculated and measured concentrations of serum ionised calcium. Of the patients whose measured concentrations of serum ionised calcium were high, 69-76% were classified as normal by the four indirect methods.

We conclude that calculation of the serum ionised calcium concentrations is not an adequate substitute for direct measurement.

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Introduction

About half the calcium in serum is bound to protein or complexed. It is the other half, ionised and biologically active, that interests the clinician, but for the past 40 years only a few research laboratories have been able to measure it. Many of the teething troubles of the Orion SS-20 ionised calcium meter have now been surmounted, which has brought this measurement within the grasp of any hospital laboratory willing to devote to it sufficient capital, running costs, and technician time.[1-3] High demand for the measurement has led a few institutions like our own, with a strong interest in renal failure and parathyroid surgery, to make the investment; in the average district general hospital the demand will be much more modest. A decision to add another financial burden to the NHS will hinge on the reliability of the available alternatives, which in ascending order of complexity are (1) uncorrected total serum calcium concentration, (2) total serum calcium with serum protein or albumin for the clinician to make an "eyeball adjustment," (3) correction of total serum calcium concentration for protein or albumin by formula, and (4) prediction of ionised serum calcium from total calcium and protein or albumin by formula or nomogram.

"Correction" of the total serum calcium concentration has been a subject of much controversy during the past two years.[4-13] Pain *et al*[14] concluded that because of the large interindividual variation a tedious procedure was necessary to calculate the correction factor individually. On the other hand, the *BMJ*[15] stated: "In specialised units newer methods for ionised calcium assay may prove valuable, but for most of us the 'corrected' plasma calcium is an adequate measure of ionised calcium on almost all occasions."

We therefore compared serum ionised calcium concentrations