Dialysis encephalopathy, bone disease and anaemia: the aluminium intoxication syndrome during regular haemodialysis

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DIALYSIS ENCEPHALOPATHY

Clinical features
Dialysis encephalopathy, now attributed to aluminium intoxication, is a complication of prolonged haemodialysis first described in 1972. Initially the condition was over-diagnosed, and at meetings of the European Dialysis and Transplant Association and the American Society of Nephrology almost half the audience claimed to have seen at least one case. In the light of subsequent studies it seems likely that many of these claims were based upon the misinterpretation of other neurological syndromes in renal failure.

However to one who has lived through an "epidemic" of this disease, the clinical picture is readily distinguished from that of most other neurological disorders. Usually the first symptom is a characteristic alteration in speech; this is partly a dysarthria due to disordered muscle action and, at the height of an attack, the tongue can be miraculously loosened by injection of diazepam. However as the disease progresses dysphasia coexists with dysarthria. Speech disturbance is initially intermittent, often precipitated by dialysis, but becomes continuous. Other early features are myoclonic jerks and grand mal seizures. Two characteristic features are dyspraxia, which affects the handwriting at an early stage, and rapid fatiguability which causes performance of all structural tasks to deteriorate within a few minutes of sustained effort. Global dementia supervenes but insight is often retained until late in the illness; this is a distressing feature since the patient has often seen his fellow patients die of the same condition and appears to know what is happening to him. In the terminal stages facial grimacing, myotonic spasms and dysphagia interfere with eating and lead to inhalation pneumonia. Death occurs from inanition, infection or deliberate withdrawal of treatment.

The major symptoms of 21 patients seen in Newcastle are shown in Table 1. Fuller descriptions of the symptomatology are contained in several recent reviews.

Table 1  Dialysis encephalopathy syndrome in 21 cases

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysarthria/dysphasia</td>
<td>21</td>
</tr>
<tr>
<td>Dementia</td>
<td>21</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>16</td>
</tr>
<tr>
<td>Seizures</td>
<td>8</td>
</tr>
<tr>
<td>Ataxia</td>
<td>8</td>
</tr>
</tbody>
</table>

Lumbar puncture has been uninformative; nearly all authors have reported normal CSF pressure, cell count and concentrations of protein, glucose and chloride. The brain atrophy to be expected in a dementing disease has been inconspicuous in the few reported studies; air encephalograms were normal in two patients and so were computerised axial tomographic (CAT) scans in 14 others. However the Chicago group found slight dilatation of the ventricles on CAT scanning in one patient and abnormal CSF dynamics, revealed by cisternography with radiiodinated human serum albumin, in seven others. Isotopic brain scans have been consistently normal.

The one laboratory test that has proved extremely useful is the electroencephalogram (EEG). A characteristic pattern of spikes and slow waves appears early in the course of the disease. After successful renal transplantation patients with early disease gradually recover (Table 2). Over the course of one or two years speech deficit diminishes but seldom disappears completely. Patients who have regained normal speech under the quiet conditions of home life become dysphasic again when embarrassed—for example, by being shown in front of a large medical audience. When patients are transplanted late in the course of the disease the downhill progress is not arrested. It is therefore crucially important to diagnose the disease at an early, reversible stage. This is difficult even when

Some of the data quoted are taken from a PhD thesis by ISP.
<table>
<thead>
<tr>
<th>Cadaver transplantation</th>
<th>No of patients</th>
<th>Aluminium concentrations (µg/g dry weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Grey matter</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>7</td>
<td>20±4 (31)</td>
</tr>
<tr>
<td>Other complications of</td>
<td>12</td>
<td>5±1 (62)</td>
</tr>
<tr>
<td>regular haemodialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uraemia (not dialysed)</td>
<td>2</td>
<td>2±9 (11)</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate the number of tissue samples analysed.
cause of dialysis encephalopathy was accepted almost at once. This rapid conversion of nephrologists owed a great deal to the dramatic account by Flendrig and his colleagues of the outbreak at Eindhoven. Two dialysis centres in the same city shared a common water supply, low in aluminium, but one of these centres was the seat of an outbreak of fatal encephalopathy which affected six patients. The source of the aluminium was traced to two aluminium anodes which were part of a cathodic protection system against corrosion in the boilers. When these anodes had been removed and the unit had moved to a new hospital a few months later, the outbreak ceased. In the United States there has been greater reluctance to accept the evidence, partly because of the authoritative opposition of Dr Allen Arieff. The alternative theories of causation have been fully reviewed by Bone but in the authors' view they are of historic interest only. However, for the sake of American sceptics the evidence for and against aluminium as the cause will be summarised.

The evidence for tissue accumulation of aluminium has been set out above. However, two other investigations have not confirmed it. Platts and Hislop found only a modest increase and Pascoe and Gregory found none, but these were small studies and the latter has only appeared in abstract. Arieff found brain aluminium concentrations in demented patients fifteen times higher than normal but rejected this as evidence of cause and effect since he also found high concentrations of aluminium in the brains of patients dying of hepatic coma, metastatic cancer and anaemia without encephalopathy. Berkseth and Shapiro found high aluminium concentrations (20-0, 17-6, 17-6, 15-6 mg/kg) in the brains of four patients who died after 32-36 months' exposure to high-aluminium dialysate, only one of whom had encephalopathy, and lower concentrations (8-6, 8-6) in two patients who died after nine months treatment on pure dialysate following four and 36 months respectively on high-aluminium dialysate, of whom one was encephalopathic. They did not feel that this evidence supported aluminium deposition in the brain as the pathogenesis of the brain lesion, though they adduced considerable epidemiological evidence for aluminium as the cause of the disease.

However, in support of Alfrey's hypothesis, a study from Rennes showed substantially higher grey matter aluminium in dialysed patients with encephalopathy than in those without encephalopathy, and further work at Denver substantiated the early results, showing almost no overlap between the encephalopathic and unaffected dialysis patients. Although the conflict of evidence is disturbing, it must be stressed that measuring brain aluminium is difficult; the most stringent precautions are necessary to exclude contamination and no publication is interpretable without full technical details. We remain prepared to pin our faith on the careful studies at Denver, Eindhoven and Rennes along with our own from Newcastle. Fortunately for our patients, if not for our scientific curiosity, the opportunity for repeating these studies is vanishing and the issue may remain unresolved.

Consequently the evidence that is likely to convince the sceptical in the long run is epidemiological. Many outbreaks have been described in association with the use of dialysis fluid with a high concentration of aluminium, usually greater than 200 µg/l. An epidemiological study of the dialysis centres in the United Kingdom showed that encephalopathy was almost unknown in those with an aluminium concentration of less than 50 µg/l in water used to make dialysis fluid, while its incidence rose progressively with higher water concentrations (Fig. 1). A similar study in France led to the...
same conclusions (Cartier F, personal communication, 1981).

A European survey conducted by the Registration Committee of the European Dialysis and Transplant Association showed that cases of dialysis encephalopathy were clustered in certain areas—the North and West of Britain, Brittany, North Spain, Greece and Scandinavia—and that 92% of these patients had been treated with dialysis fluid made from unprocessed or softened water.44 In many of the outbreaks referred to earlier in this paragraph, the introduction of a deioniser or a reverse osmosis system abruptly ended the "epidemic." In Newcastle cases of overt encephalopathy stopped occurring just before the changeover to a purified water supply. This was due to the suspension of home dialysis in Cumbria, the worst affected area of the region, because patients were dying at such an alarming rate; although the Newcastle water supply gave rise to a few cases of encephalopathy, the incubation period was long and the incidence low.

The protective effect of good water treatment has been maintained as reported from Plymouth42 and Sheffield43 and from several other centres (AM Pierides, personal communication 1981). In Newcastle only one new case of encephalopathy has appeared since the introduction of purified water; this patient's home water treatment system was not removing aluminium adequately. One other patient, heavily exposed to aluminium before reverse osmosis was installed, suffered some progression of his encephalopathy afterwards, in keeping with experience after transplantation in such patients. The all but universal success of precautions against aluminium exposure in eliminating this disease is the strongest argument supporting aluminium overload as the sole cause. However it has to be acknowledged that water treatment removes many other potentially toxic substances. Of these, only manganese has some small claim to an epidemiological association with the disease54 and has been found in excess in the brains of affected patients,92 though in the white matter rather than in the histologically involved grey matter.

Some supporting evidence for the role of aluminium comes from the association between encephalopathy and high concentrations of aluminium in tissues other than brain, notably bone (discussed below) and serum or plasma (Fig. 2). The considerable overlap in most studies between the plasma aluminium concentrations of patients with encephalopathy, and those treated at the same centre who have not yet developed the disease,40, 46–48 is not surprising; plasma aluminium, which reflects recent exposure to a source of aluminium overload, usually the dialysate (Fig. 3), takes a few weeks to change when water purification is introduced.41 Cerebro-

![Fig. 2](image-url) **Fig. 2** Serum aluminium (Al) in haemodialysis patients, showing high aluminium levels in bone disease and encephalopathy (for methods see reference 33).

![Fig. 3](image-url) **Fig. 3** Serum aluminium (Al) in patients on regular haemodialysis on different forms of water treatment. Measurements were made immediately before dialysis.
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spinal fluid aluminium has received little attention but appears to have a closer association than plasma aluminium with the presence of encephalopathy. The total body burden of aluminum cannot be measured easily, but can be estimated from whole body neutron activation; it is raised by several grams in patients with encephalopathy.

**Dialysate aluminium**

With one exception, all published outbreaks of encephalopathy have been traced to aluminium contamination of the dialysis fluid. The unusual source of aluminium at Eindhoven has been described above; the commoner source is treatment of surface water by the water authority to remove organic materials affecting its colour and taste. The first stage of this process is flocculation. Aluminium sulphate is a popular flocculating agent since the residue of alum which remains after the process does not affect either the colour or the taste of water. This residual aluminium content varies from day to day (Fig. 4) reflecting weather conditions which affect the organic content of the water. The chemical formulation of residual aluminium also varies; it changes from aluminium salts through colloidal particles to aluminates as the pH rises. The solubility curve is therefore U-shaped (Fig. 5). Although the

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**Figure 4** Effects of softening, deionisation and reverse osmosis on aluminium (Al) content of Newcastle tap water.

**Figure 5** Effect of pH on the proportion of ionised aluminium (Al) in Newcastle tap water (4 samples).
resins of water softeners have a high affinity for aluminium they do not remove it reliably from water supplies (Fig. 4).21 34 36 42 44 56–58 Deionisers are much more effective and have often been sufficient to halt an outbreak. In Sheffield they have even permitted improvement of affected patients.34 35 However they are not totally reliable in all water supplies (Fig. 4). Twin bed deionisers seem likely to be more effective than mixed bed deionisers. Reverse osmosis has been consistently effective in Newcastle (Fig. 4) but there have been occasional exceptions elsewhere.53 The best arrangement is a water softener, reverse osmosis and deioniser in series; the cost is fully justified in areas with high tap water aluminium.41 Whatever system is chosen, it should be tested on the local water supply and monitored regularly.

When dialysate pH is carefully controlled at close to 7·0 much of the aluminium is in colloidal form, and at this pH, dialyser clearance was found to be low,54 at least in vitro. The importance of dialysis fluid pH is emphasised by the Redy system of dialysate regeneration* which releases more aluminium from the cartridge when used with bicarbonate-containing dialysis fluid than with the usual acetate solution.56 However, most studies of dialysate aluminium clearance in vivo have shown results similar to those in Fig. 6, which imply that much of the dialysate fluid aluminium is in solution. There is rapid uptake of aluminium by the blood unless the dialysate concentration is kept down to about 10 μg/l.52 56–58 In Newcastle, the use of water purified by reverse osmosis enabled zero aluminium balance across the dialyser to be achieved, but not its removal from the blood; the slight rise during dialysis shown in Fig. 7c is accounted for by haemoconcentration, since serum aluminium is about 80% protein bound.59 However, Graf and his colleagues, using very pure water and treating patients with higher initial serum aluminium concentrations than in the Newcastle patients have achieved some aluminium removal from the body by dialysis.59 60

Oral aluminium

Studies in the early 1970's reported hyperaluminacemia from ingestion of aluminium-phase resins,61 and positive aluminium balance from ingestion of aluminium hydroxide;62 however the methods used for measuring aluminium grossly exaggerated the amount of aluminium absorbed and would not now be acceptable. Nevertheless the results have proved qualitatively correct. Alfrey's group assumed that ingested aluminium was the major source of the
overload in dialysis encephalopathy and soon showed by sensitive techniques that even normal subjects had a rise of serum aluminium within a few days while ingesting aluminium hydroxide. This has been confirmed for patients in chronic renal failure who were not on dialysis or were dialysed against very low concentrations of aluminium. In general the serum concentrations attained in these studies have been well below those found in patients with encephalopathy (Fig. 7). A survey conducted by

![Graph](http://jcp.bmj.com/)

**Fig. 7** Serum aluminium (Al) in normal subjects and subjects with chronic renal failure not treated by dialysis.

the Registry of the European Dialysis and Transplant Association found no correlation between oral intake of aluminium hydroxide and incidence of dialysis encephalopathy. Tens of thousands of patients have taken aluminium hydroxide to control plasma phosphate in chronic renal failure without developing encephalopathy. Consequently it has now been generally assumed that the risk of dangerous aluminium overload from this source is small or negligible.

However there are a few disturbing facts that leave a question mark over the safety of oral aluminium in renal failure. One large outbreak of encephalopathy involved 13 patients who were dialysed against very low concentrations of aluminium. This event was so unusual that some other source of aluminium overload, not yet revealed by the careful investigations at Nashville, must be suspected. Several other isolated cases or small outbreaks have been attributed to aluminium ingestion but must be accepted with some reserve since the patients were dialysed against fluid which contained 50-80 \( \mu \text{g/l} \) of aluminium or was of unstated aluminium content. Even if these cases are discounted as unproven, there remains a hard core of published cases which are difficult to dismiss. At least four patients have developed “dialysis encephalopathy” without ever being dialysed. In another patient, a rise in serum aluminium and the appearance of symptoms coincided with oral aluminium administration on two occasions. In one outbreak encephalopathy stopped occurring, and affected patients improved, when oral administration of aluminium was discontinued, without any reported change in dialysis conditions. A few patients in Newcastle have developed very high plasma aluminium concentrations after prolonged administration of aluminium hydroxide for stable chronic renal failure. Different preparations of aluminium hydroxide and other compounds differ in their ability to bind phosphate or release aluminium. It is concluded that oral administration of aluminium hydroxide is a rare cause of serious aluminium overload and that patients in renal failure receiving large doses over long periods should have regular checks of serum aluminium.

**Treatment**

This disease is easier to prevent than to treat. The beneficial effects of transplantation at an early stage have been mentioned above. Impressive reversal of early disease has been achieved also by rigorous exclusion of aluminium from the dialysis fluid and oral medications. However there was little to offer the patient with well developed disease until the introduction of chelation therapy by Ackrill and his colleagues. The effectiveness of desferrioxamine in removing tissue aluminium has been confirmed indirectly by others but there are no published data so far on direct tissue measurement, and only preliminary information on changes in cerebral function. The striking improvement in handwriting and other tests of constructional ability in patients with moderately severe disease treated by removal of the source of aluminium gives ground for some optimism.

**Associated Features**

**Bone disease**

Osteomalacia, diagnosed histologically, affects about 20% of patients in terminal renal failure. In general, treatment with regular haemodialysis and vitamin D analogues heals or improves most of these patients but it has become apparent in the last 13 years that some dialysis centres were characterised...
by progressive development of a severe form of osteomalacia causing bone pain, fractures, severe deformity and myopathy, in which serum alkaline phosphatase was usually normal or low, serum calcium was sometimes high and readily raised by administration of calcium or vitamin D, and the bone lesion was unresponsive to vitamin D or its newer analogues. In Europe the disease has become known as “Newcastle bone disease” because of its high incidence in Northern England and our interest in the topic. Fuller descriptions of the syndrome, and the evidence that it is caused by aluminium in bone, have been presented elsewhere. Two recent advances in understanding have been the reproduction of the disease in rats by aluminium administration and the application of histochemical stains for aluminium, which have been verified by other techniques and which have shown aluminium localised in the mineralising layer of the osteoid. It is now possible to recognise the disease with some confidence from a simple undecalcified bone biopsy without the considerable effort required to measure bone aluminium by neutron activation.

Papers continue to appear from the United States describing this form of bone disease and containing statements like “the cause of this severe osteomalacia, which occurs despite normal or slightly elevated levels of serum calcium and fails to mineralize with calcitriol, is unclear.” It is suggested that the evidence presented or reviewed in the articles quoted above makes it extremely likely that “this severe osteomalacia” is another manifestation of aluminium overload.

Anaemia
Patients with dialysis encephalopathy are generally sick. They often lose weight and look ill. It is likely that several tissues other than brain and bone are affected. A microcytic anaemia is associated with dialysis encephalopathy and remits when exposure to aluminium is reduced. It may prove to be a useful early warning of the syndrome since in an Edinburgh series it preceded clinical evidence of bone disease and encephalopathy in many of the patients.

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