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Multiorgan aluminium deposits in a chronic haemodialysis patient

Electron microscope and microprobe studies

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Summary. The study reports an aluminium-intoxicated haemodialysis patient who had encephalopathy, osteomalacia and congestive cardiomyopathy prior to his death. Detailed light and electron microscope examination revealed the presence of aluminium deposits within lysosomes of cells from many organs, including the kidney, liver, brain and heart. The heavy aluminium deposits in myocardial lysosomes favor a possible role of the trace element in the patient's congestive cardiomyopathy.

Key words: Aluminium-intoxication – Haemodialysis – Encephalopathy – Cardiomyopathy – Lysosomes

The finding of increased cerebral aluminium (Al) concentrations in haemodialysis patients who had died from progressive myoclonic encephalopathy led Alfrey et al. (1976) to the hypothesis of a possible aetiological role for the trace element Al in this severe disease. Previously Lapresle et al. (1975) reported a case of progressive encephalopathy where Al was detected in the brain by electron microprobe analysis. The localization of Al in the grey matter of the brain has been interpreted as evidence for a predominant role for this trace element in a particular particular type of encephalopathy (Galle et al. 1979). In most organs studied, Al deposits are found intracellularly within lysosomes (Galle 1974).

Experimentally, neurofibrillary degeneration has been induced by repeated intracerebral injections of aluminium phosphate in rabbits (Klatzo et al. 1965). However, it must be stressed that most often post mortem studies of brains from uraemic patients with dialysis encephalopathy have revealed no abnormality on light or electron microscope examination (Terry and Pena 1965). Thus, several clinical and experimental arguments have accumulated that favour a role of Al in the pathogenesis of dialysis-related

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encephalopathy, but definite proof for its responsibility has not yet been provided.

The present post mortem study, in a haemodialysis patient with myoclonic encephalopathy shows, in agreement with previus reports, that Al can be localized in the lysosomes of the brain, liver and kidney using electron microprobe and electron microscope (Galle 1974; Galle et al. 1979; Galle and Giudicelli 1982; Galle et al. 1980; Galle and Berry 1980; Galle 1981).

In addition, the study demonstrates the existence of multiorgan involvement and focuses in particular on myocardial Al deposits.

Case report and methods

A 61-year-old male with a previous history of polycystic kidney disease and arterial hypertension who had received regular home haemodialysis treatment for 10 years developed convulsive myoclonic encephalopathy, osteomalacia, congestive cardiomyopathy with cardiomegaly and hepatitis (HBs antigen +) with hepatomegaly. Congestive cardiomyopathy was characterized by increased left ventricular end-diastolic volume and pressure and a decreased ejection fraction on left heart catheterization. No coronary artery stenosis was observed. Iliac bone biopsy confirmed osteomalacia, with five-fold increase in osteoid volume and surface and impaired mineralization. Plasma aluminium concentrations assessed by flameless atomic absorption spectrometry using a graphite oven were 20–30 times normal levels, demonstrating aluminium intoxication. Bone aluminium concentration was 38 μg/g (wet weight) at time of biopsy and 58 μg/g at time of death, one year later. Myocardial aluminium concentration at autopsy was 5.4 μg/g (wet weight).

During the last year of life, encephalopathy and congestive cardiomyopathy had progressively increased in severity and eventually led to death. The following findings were made at autopsy performed 17 hours after death:

1. Macroscopic findings

– The kidneys are polycystic but only slightly hypertrophied (right kidney 220 g, left kidney 200 g, vs. 150 g normal), without haemorrhage or pus. Localization of cysts is restricted to the kidneys since no such lesions are observed on the liver surface or that of the pancreas or the prostate.
– Congested nutmeg liver, without cirrhotic nodules, weighing 2,370 g (vs. 1,400 g normal weight).
– The heart is hypertrophied with left ventricular wall thickening but not dilated and weighs 650 g (vs. 270 g normal weight). No thrombosis or coronary stenosis is observed. No evidence of infarct, endocarditis, myocarditis or fibroelastosis is present. The aorta and pulmonary vessels and the heart valves and chordae are normal.
– The brain weighs 1,060 g (normal, 1,300 g). Its exterior aspect and that of the cut surface are normal. There is no necrosis, meningeal or ventricular haemorrhage, calcification, thrombosis, stenosis, vascular anomaly or tumor.
– The four parathyroid and the thyroid glands are normal.
– Bronochopneumonia, characterized by the presence of disseminated haemorrhagic and purulent infiltrates in the parenchyma and the bronchial tree, is observed in the lungs, which are severely congested. The right lung weighs 780 g (normal 350 g) and the left 500 g (normal 320 g).
– Dorsal vertebrae were subjected to a decalcification procedure.

2. Microscopic findings

Samples for light microscopy were fixed in 15% formaldehyde, embedded in paraffin and stained with hematin eosin safran (HES).

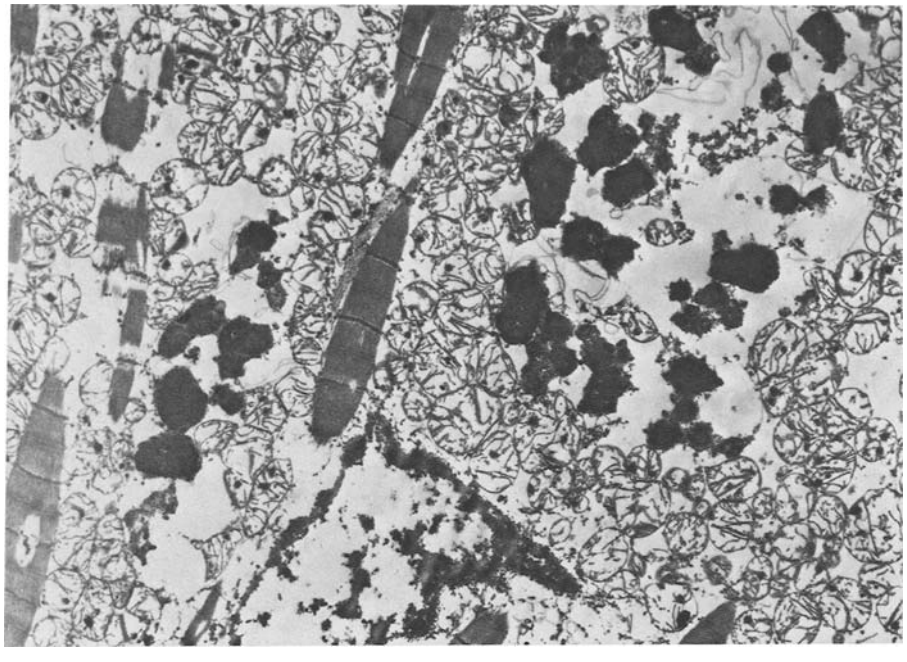

Fig. 1. *Myocardiac sample.* Intracytoplasmic deposits. Dense heterogeneous granulations which accumulate in the cytoplasm between the myofibrils. Interpretation of the mitochondrial alterations and the fragmentation of the myofilaments is difficult in the context of pre- and post mortem cell damage. × 8,000

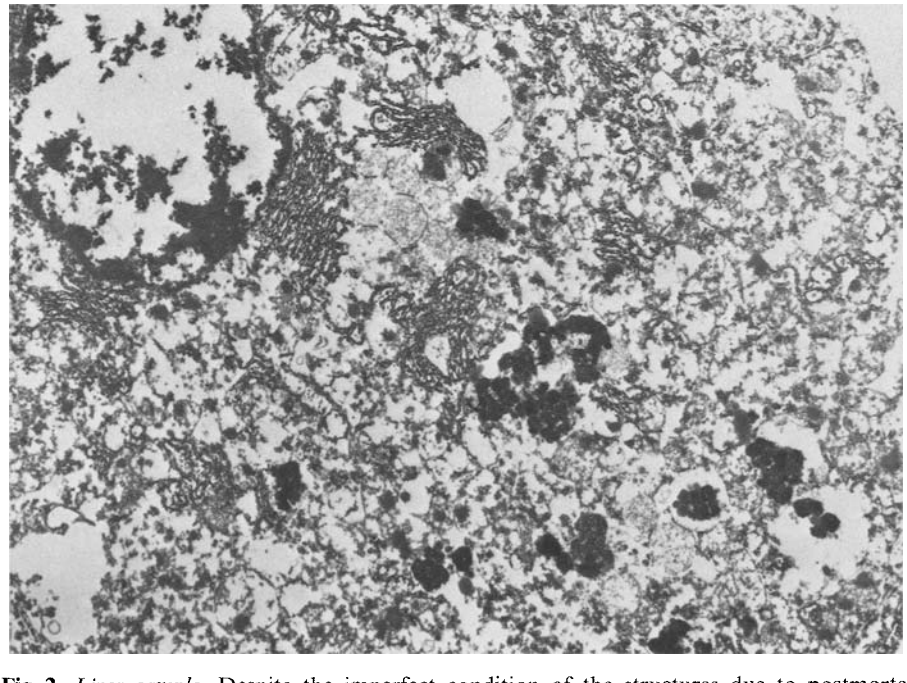

Fig. 2. *Liver sample.* Despite the imperfect condition of the structures due to postmortem lysis, dense, granular intracytoplasmic deposits can be seen. × 9,000

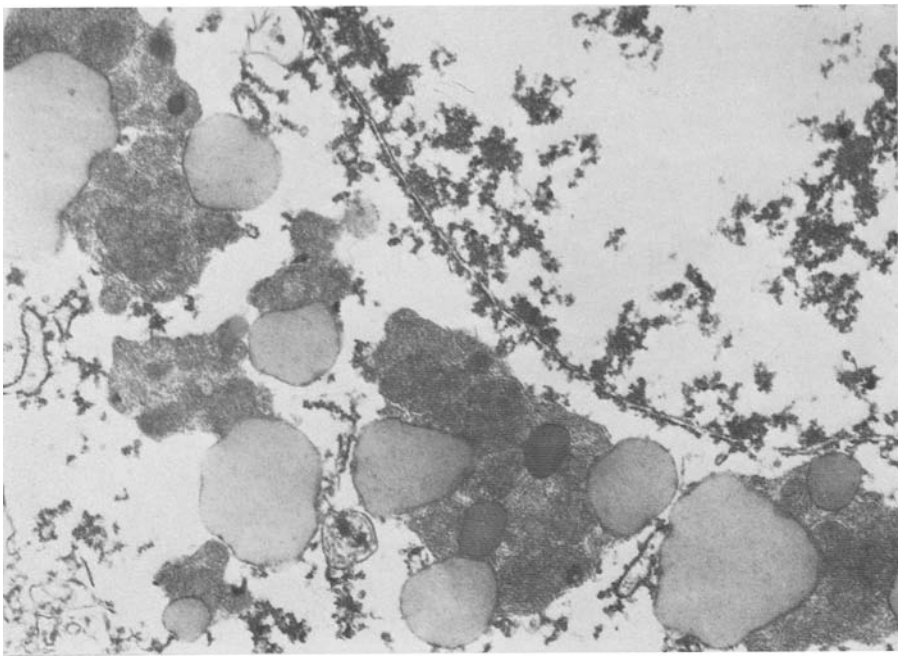

Fig. 3. *Brain sample.* Presence of heterogeneous granular deposits associated with lipid-like areas of lighter density. Lysosomal residue which accumulates in the perinuclear cytoplasm. ×20,000

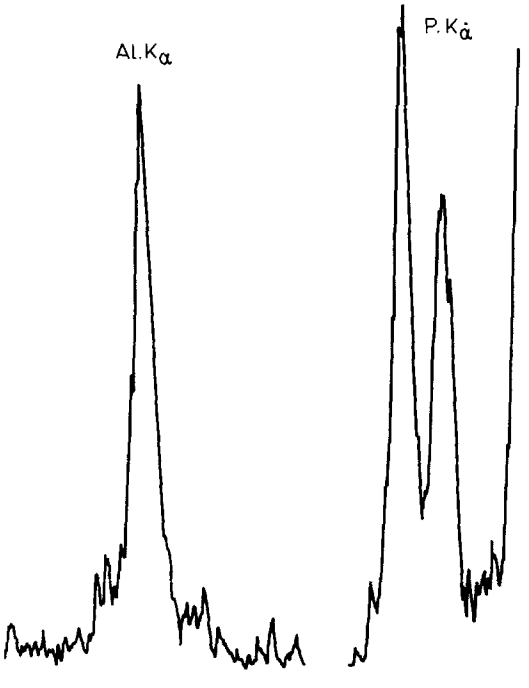

Fig. 4. Characteristic X ray of aluminium Al_{Ka} and phosphorus P_{ka} emitted from one dark lysosome observed on Fig. 1. The spectrometer used in the Camebax microprobe is a wave-length dispersive machine

Samples for electron microscopy study were fixed in glutaraldehyde, postfixed in osmium tetra-oxyde and then embedded in epon-araldite. Ultrastructural study was performed on ultrathin sections placed on copper grids without subsequent treatment with uranyl salts or lead citrate.

X-ray microanalysis was performed on the same ultrathin sections with a Camebax microprobe coupled with a conventional transmission electron microsope.

Results

1. Light microscopy (HES staining)

– The kidneys are totally polycystic (bilateral polycystic kidney disease). The cyst fluid is haemorraghic without pus or organisms. The few remaining tubules are compressed and most of the few residual glomerules are fibrotic. There are no glomerular deposits. The vessels are not thrombosed and vascular walls are normal.
– The liver has a typical congestive appearance, with congested centrolobular veins, oedema, haemorrhagic suffusion and hepatocyte necrosis around the centrolobular veins, associated with dilation of the neighbouring sinusoid vessels.
– No cardiac lesion is observed. No necrosis, myo- or endocardial infiltrative process. No coronary thrombosis or infiltrates. No calcium deposits (von Kossa stain), no haemochromatosis (negative Perls stain), no amyloidosis (negative Red Congo stain in polarized light).
– The lungs are the site of a severe fibrinoleukocytic bronchopneumonia, without necrosis, viral inclusions or plasmodial cells, and without bacteria, parasites or mycelium.
– The thyroid and the four parathyroid glands are normal, without hyperplasia or adenoma.
– The bones have an osteomalacic aspect with few osteoblasts or osteoclasts and increased osteoid lamellae.
– The brain (neurons, neuroglia and plexus) show no lesions.

2. Ultrastructural study and analytical ion microscopy

– Usual electron microscopy discloses voluminous granular deposits of varying electron intensity, localized within cell lysosomes of the renal epithelial tubules, the glomerular mesangium, the hepatocytes (but not in Kupffer cells), the neurons (but not in glail cells) and in the cardiac myocytes.
– X-ray microanalysis of these lysosomes observed in the heart (Fig. 1), liver (Fig. 2) and brain (Fig. 3) demonstrated a high concentration of aluminium and phosphorus (Fig. 4).

Discussion

According to Galle et al. (1980), the aluminium found in the normal human body largely comes from dust in the air (clay, aluminium silicates, and vermiculites). These particles are taken up by alveolar macrophages and

partially degraded and then eliminated in the urine, except in the case of chronic renal failure. The dialysis fluid used for the haemodialysis procedure and the aluminium gels given to dialysis patients appear to be the main sources of aluminium excess during chronic renal failure, as shown by various authors (Alfrey et al. 1976; Buge et al. 1979; Cartier et al. 1978; Flendrig et al. 1976; Platts and Hislop 1976).

Aluminium is known to be toxic to several organs. In bone, low-turnover osteomalacia seems to be caused by massive Al deposits at the mineralization front. Alumium deposits in the liver are frequently observed (Berlyne et al. 1970; Flendrig et al. 1976; Flendrig et al. 1976; Galle and Giudicelli 1982; Kushelevsky et al. 1976). Most often, they are not associated with a liver pathology. However, massive intracellular deposits may be observed in some cases and they are associated with severe lesions of the hepatocytes. In addition, alumium induces microcytic anaemia and leukocytosis (O'Hare and Murnaghan 1972; Siebert and Wells 1929). The experimental injection of Al can induce porphyria leading to hepatic lesions (Kushelevsky et al. 1976; Sears and Eales 1973) and microcytic anaemia in the uraemic rat (Touam et al. 1983).

Aluminium toxicity in the brain has been the most studied. Alfrey (1976) found increased levels of aluminium in the neurons of the cortex in dialysis patients who died from progressive myoclonic encephalopathy. This finding confirms the data reported by Lapresle et al. (1975) demonstrating by electron microprobe the presence of high concentrations of aluminium in the brain of a patient who had died of progressive myoclonic encephalopathy of undetermined origin. Similarly, Ducket and Galle (1976) showed the presence of aluminium in senile plaques of three patients who had die of Alzheimer's disease, and in the pallidum of five patients who had died of Parkman's disease (1976). Many authors accept the hypothesis of a causal relationship between aluminium and encephalopathy (Buge et al 1978; Buge et al. 1979; Chokroverty et al. 1976; Masbernard et al. 1977; Platts and Hislop 1976; Poisson et al. 1978). Experimental intoxication of rats by aluminium also appears to induce encephalopathy (Duckett and White 1974; Duckett and White 1974; Galle et al. 1980; Klatzo et al. 1965; Terry and Pena 1965), but the existence of encephalopathy in the animal is extremely difficult to prove. One can distinguish two types of human encephalopathy schematically. The first occurs after inhalation or ingestion of abnormally high quantities of aluminium, as reported by Petri as early as 1930 (Petri 1930) and then by others (Alfrey et al. 1976; Berlyne et al. 1972; McLaughlin et al. 1962; Poisson et al. 1978). The second type occurs without apparent contact with aluminium, when the metal is found in the brain (Crapper et al. 1976; Duckett and Galle 1976; Duckett et al. 1976; Lapresle et al. 1975). Human encephalic lesions in dialysis patients consist of loss of neurons, which are replaced by fibrillary structures and lipofuscin deposits (Duckett and White 1974). The experimental injection of aluminium salts into rat brain does not alter the brain morphologically (Levine and Sowinski 1978); however, repeated subcutaneous and intraperitoneal administration of aluminium salts induces the destruction of brain neurons in rats, rabbits,

cats and dogs (Klatzo et al. 1965; Scherp and Church 1937; Terry and Pena 1965; Wisniewski et al. 1970).

The intracellular localization of aluminium is essentially lysosomal (Galle 1974). Analytical ion microscopy shows that alumium is deposited in the lysosomes of brain neurons (not of the glia) and of hepatocytes (not of Kupffer cells). Only rarely are these lysosomal deposits accompanied by deposits in mitochondria and ribosomes. It is also possible that infinitely small quantities of aluminium are localized in nuclei, as suggested by De Boni et al. (1976), who injected rabbit brain with aluminium salts and used a fluorescent technique with pentahydroxyflavon staining. Previously, Miller and Levine (1974) had demonstrated aluminium salts in the nuclei of neuroblastoma cell cultures. Sabouraud et al. (1978) confirmed this localization and Truchet (1976), using analytical ion microscopy, observed aluminium salts in cell nuclei.

Aluminium is deposited in the lysosomes by precipitation of aluminium salts (Hager 1968). Using microprobe analysis, such lysosomal deposition of mineral salts was shown by Galle for uranium and gold in the proximal tubular cells of the nephron (1974), by Ducket and White for tellurium in the neurons (1974) and by Berry et al. for chromium in the proximal renal tubule (1978). Aluminium could also be deposited in the mitochondria, as suggested in recent personal work in the bone of haemodialysis patients by Plachot et al. (1984 in press).

The mechanism of this salt precipitation, according to Galle and Berry (1980) could be 1) active protein transport of the lysosomal membrane which concentrates aluminium and precipitates negative anions when the solubility threshold has been reached; or 2) via acid phosphatase activity, which induces precipitation in the form of aluminium phosphate. Whatever the actual mechanism, the daily intraperitoneal injection of aluminium chloride (10 mg/0.5 ml) to Wistar rats sacrificed one month later induces aluminium salt precipitation in the lysosomes of cortical brain neurons. Lysosomes can also actively concentrate many mineral elements other than aluminium, such as uranium, indium, gold, tellurium, iron copper, zinc mercury, lead, cobalt, cadmium, and plutonium (Galle 1974; Galle et al. 1979; Galle and Giudicelli 1982; Galle et al. 1980; Galle and Berry 1980).

In addition, Ducket et al. (1977), Sternlieb and Goldfischer (1976) suggest that aluminium precipitates in the form of phosphate salts which concentrate in the lysosomes, leading to the formation of lipofuscin granules and eventually to the destruction of neurons.

Intralysosomal precipitates of aluminium phosphate have also been found in the kidneys (tubular epithelial cells), the bone (aluminium osteomalacia, mitochondrias of osteoblasts), the hepatocytes and the brain neurons.

We also found precipitation of aluminium salts in cardiac myofibrils, which may be the cause of the congestive cardiomyopathy. In fact, the cause(s) of congestive cardiomyopathy in the haemodialysis patient are not known (Drueke et al. 1981). The fact that most patients in whom severe congestive cardiomyopathy has been diagnosed were not affected by encephalopathy does not favour a unique role for aluminium in this severe

heart disorder. Whether and by what mechanism severe aluminium loading of cardiac myocytes interferes with myocardial function remains to be elucidated by further studies.

There was no morphologically evident hyperparathyroidism, at least at the time of death. It could thus be concluded that hyperfunction of the parathyroid glands did not play a role in the occurrence of the aluminium deposits. However, it is also possible that earlier hyperparathyroidism was secondarily repressed by the effect of aluminium intoxication, after having first favoured the accumulation of aluminium in the organism, as suggested by Mayor et al. (1978). The question whether other still unknown factors have favoured the heavy aluminium deposits in the cardiac myocytes of this patient cannot be solved at the present state of knowledge.

Conclusion

This observation in a 61-year-old dialysis patient who died of progressive myoclonic encephalopathy with cardiomyopathy, shows multiorgan intoxication by intralysosomal aluminium phosphate salts, detected by analytical ion microscopy. Osteomalacia secondary to aluminium intoxication had already been diagnosed by quantiative bone histology during the life of the patient. Autopsy confirmed lysosomal aluminium intoxication, not only in the tubules and mesangial cells but also in the neurons of the brain, the hepatocytes and the cardiac myofibrils. The congestive cardiomyopathy of at least some dialysis patients could be due to aluminium intoxication.

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