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# MICROCYTIC ANAEMIA: A MARKER FOR THE DIAGNOSIS OF ALUMINIUM TOXICITY

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## Summary

Microcytic anaemia without iron deficiency is described in aluminium intoxication due to oral aluminium ingestion in long-term dialysis patients. Treatment with desferrioxamine to mobilize and remove aluminium has been compared in two groups of patients with aluminium accumulation, one group with and one without microcytosis. Desferrioxamine therapy stabilized or improved the bone and neurological symptoms associated with aluminium toxicity in both groups, but desferrioxamine increased the mean corpuscular volume and improved the anaemia only in the microcytic group. The haematological improvement in microcytic patients corresponds temporally with relief of bone pain and muscle weakness, and also correlates significantly with the degree of aluminium burden as indicated by the pre-treatment serum aluminium and by the peak serum aluminium during chelation. It appears that aluminium interferes with haem synthesis and leads to microcytosis in some patients, representing an easily detected objective marker for aluminium toxicity and the response of aluminium toxicity to treatment.

## Introduction

The association between dialysis encephalopathy and excess aluminium in water used for haemodialysis [1–3] has prompted widespread use of water treatment procedures to eliminate contaminant aluminium. Aluminium removal from dialysate appears to prevent epidemic incidence of encephalopathy and associated bone disease, and to allow some patients who have the syndrome to stabilize or improve [1,3]. However, the syndrome of aluminium toxicity, manifesting as osteomalacia with or without encephalopathy, continues to occur among long-term dialysis patients. The major source of aluminium exposure in such patients is now believed to be the phosphate binding antacid medications which contain large amounts of $Al(OH)_3$, with clear correlation between the

accumulated aluminium burden and the duration of long-term dialysis with the use of such antacids [2].

At the University of Michigan we have a large group of patients who have been on dialysis for up to 16 years, and clinical abnormalities attributable to aluminium accumulation are an ongoing problem. In addition to bone and neurological abnormalities, we have noted microcytic anaemia not associated with iron deficiency, but associated with a detectable aluminium burden and reversed with desferrioxamine chelation. This microcytic anaemia has been briefly noted in prior reports [3–6] but has not been investigated in detail.

## Patients and methods

In our dialysis population of 120 patients, eight patients were identified with a mean corpuscular volume persistently below 80 cubic microns not attributable to the usual known causes of microcytosis. Iron deficiency was ruled out by evaluation of serum iron and iron binding capacity, serum ferritin, and bone marrow sampling where necessary. When necessary, screening for lead accumulation and thalassaemia were performed.

These patients with microcytosis were suspected of suffering aluminium toxicity because of clinical symptoms consistent with aluminium intoxication and concomitant evidence for aluminium accumulation. For comparison, another group of patients was identified with similar evidence for aluminium accumulation but without microcytosis.

The microcytic patients did not differ significantly from the normocytic group in age, in the long duration of prior dialysis or in the large amount of cumulated antacid ingestion. The patients in both groups all had progressive bone pain, with six of eight microcytic and five of five normocytic patients having additional objective evidence of proximal muscle weakness. However, most of these cases had little objective evidence for hyperparathyroidism to explain these symptoms. Bone X-rays showed osteopenia and pathological fractures in several cases, but minimal subperiosteal bone resorption in only two microcytic cases. Alkaline phosphatase and N-terminal parathyroid hormone were only mildly elevated on average, not differing between the two groups and exceeding twice the normal value in only two microcytic patients.

Neurological abnormalities consistent with aluminium intoxication were found in both groups, including speech pathology in all eight microcytic and in four of five normocytic patients. Additional myoclonus and/or seizure activity with characteristic EEG changes were present in three of eight microcytic but in no normocytic patients, suggesting that more severe neurological changes may characterize the microcytic group.

The suspected diagnosis of aluminium toxicity was confirmed by serum aluminium over 100μg/L and/or increase in serum aluminium by more than 200μg/L after desferrioxamine infusion [7], with bone biopsy employed only when the diagnosis was still in doubt. Seven of the microcytic cases and five normocytic cases have undergone desferrioxamine therapy for more than two months and will be reported comparatively.

Patients in both groups received 20mg/kg desferrioxamine thrice weekly, during the last two hours of each treatment for haemodialysis patients and in the overnight exchange three nights weekly for continuous ambulatory peritoneal dialysis (CAPD) patients. Serum aluminium was measured by atomic absorption on freshly spun and frozen serum collected in specially washed tubes, drawn just before a dose of desferrioxamine.

## Results

Table I shows that the serum aluminium before desferrioxamine was similar in both groups, averaging 246μg/L in the microcytic patients and 225μg/L in the normocytic patients. Serum aluminium concentrations increased significantly during desferrioxamine therapy in both groups, but the maximal increase in serum aluminium for the microcytic group of 400μg/L was significantly greater than that for the normocytic group of 218μg/L. The peak in serum aluminium occurred within two months of starting therapy in all cases but one, and serum aluminium declined progressively thereafter in all cases in both groups.

TABLE I. Results of desferrioxamine treatment

| | Serum aluminium (μg/L) | | Mean corpuscular volume ($mic^3$) | | Haematocrit (vol %) | | Free erythrocyte protoporphyrin (μg/L) | |
|---|---|---|---|---|---|---|---|---|
| | Pre | Dur | Pre | Dur | Pre | Dur | Pre | Dur |
| Microcytic | 246 ±173 | 646 ±435 | 68.0 ±8.7 | 88.0 ±11.5 | 23.8 ±3.3 | 36.0 ±5.4 | 75.1 ±24.6 | 46.7 ±21.8 |
| *p< | 0.01 | | 0.01 | | 0.001 | | 0.05 | |
| **p< | 0.01 | | 0.001 | | 0.01 | | 0.10 | |
| Normocytic | 225 ±203 | 453 ±210 | 90.0 ±4.2 | 95.0 ±5.7 | 23.4 ±6.7 | 28.0 ±8.5 | 45.6 ± 6.2 | 40.7 ±16.7 |
| *p< | 0.05 | | 0.10 | | NS | | NS | |

* Student's 't' test comparing 'Pre' (pre-treatment) to 'Dur' (maximal change during treatment) for each indicator, in each group

** Student's 't' test comparing the change from 'Pre' to 'Dur' in the 'microcytic' group to the change in the 'normocytic' group for each indicator

Bone pain was markedly improved within two to four months of initiating treatment in six of seven microcytic patients and in three of five normocytic patients. Proximal muscle weakness was significantly improved by objective examination within the same time period in five of six microcytic patients and in two of five normocytic patients. Long-term stabilization or improvement in neurological findings characterized both groups, even with the more severe abnormalities in the microcytic group.

Table I shows that the maximal change in mean corpuscular volume noted

during desferrioxamine therapy was striking in microcytic patients, all seven cases becoming normal within five months of starting treatment. In normocytic cases, mean corpuscular volume rose slightly but not significantly. Table I shows that haematocrit values also increased strikingly among the microcytic patients, with sustained increases ranging from five to 19 vol %, averaging 12 vol %, and occurring within five months of initiating therapy. In contrast, the mean haematocrit did not change statistically in the normocytic group, although two individual cases did show increases of eight and 19 vol %, respectively.

Normalization of mean corpuscular volume and improvement in haematocrit among the microcytic patients occurred despite significant reduction in serum ferritin from an average of 199ng/dl to 53ng/dl ($p<0.001$), thus excluding iron deficiency as a cause of the original microcytosis. Three microcytic patients eventually required iron supplementation when serum ferritin levels decreased below 50$\mu$g/L, but maximal mean corpuscular volume and haematocrit changes reported here had already been attained before this supplementation. Table I demonstrates the associated finding of elevated free erythrocyte protoporphyrins before therapy among the microcytic cases, with significant reduction during desferrioxamine. In contrast, the mean free erythrocyte protoporphyrins among normocytic patients was normal before therapy and did not change significantly during desferrioxamine. This abnormality in free erythrocyte protoporphyrins signals a metabolic defect in haem synthesis which reversed with desferrioxamine treatment.

The improvement in microcytic anaemia corresponded temporally with mobilization and removal of aluminium and with improvement in bone and muscle findings attributable to aluminium toxicity. More important, Figure 1 shows that the improvement in haematocrit also correlated with the magnitude of the aluminium burden as indicated by both the serum aluminium before desferrioxamine as well as the peak serum aluminium concentration during chelation. Furthermore, Figure 1 shows that the normalization in mean corpuscular volume during aluminium removal also correlated significantly with the aluminium burden in the same manner. Similar correlation of the decrease in free erythrocyte protoporphyrins with serum aluminium before treatment ($r=-0.92$, $p<0.001$) and with peak serum aluminium during therapy ($r=-0.84$, $p<0.001$) was also noted. These correlations, along with the clinical improvement during treatment, implicate aluminium as a toxic cause of the microcytic anaemia.

## Conclusions

Despite the widespread use of water treatment by deionization or reverse osmosis methods in haemodialysis facilities, the syndrome of aluminium toxicity continues to plague long-term dialysis patients who ingest large quantities of antacids containing aluminium as a phosphate binder. Osteomalacia and encephalopathy are well recognized components of this syndrome, but anaemia has been recognized only as a possible concomitant of aluminium toxicity [3–6]. The present report offers objective evidence that microcytic anaemia is also an important component of the toxic syndrome in humans, probably resulting from interference of aluminium with haem synthesis described in vitro [8,9] and suggested

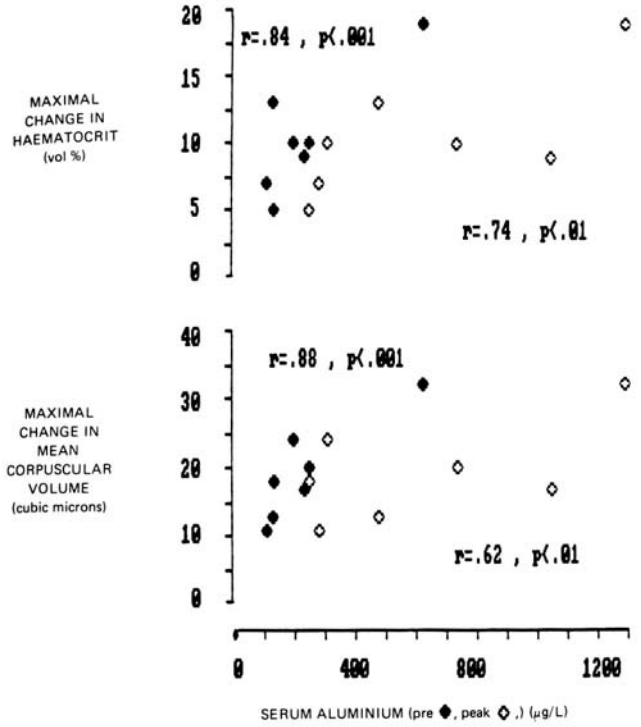


Figure 1. Linear regression analysis of haematocrit (upper panel) and of mean corpuscular volume (lower panel) versus both the serum aluminium before therapy (closed symbols) as well as the peak serum aluminium (open symbols) during desferrioxamine. The correlation coefficients and p values in the upper lefthand corner of each panel refer to the pre-treatment values and those in the lower righthand corner of each panel to the peak values

by the development of microcytic anaemia with aluminium in rats [10]. Furthermore, it appears that microcytic anaemia may be an important marker for more severe aluminium toxicity. Improvement in microcytosis during desferrioxamine therapy represents an objective indicator of the overall response to therapy and further proves the toxic role of aluminium in this syndrome.

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