Aluminum-induced microcytic anemia in experimental chronic renal failure

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RESUMEN

Anemia microcítica secundaria a intoxicación alumínica en la insuficiencia renal crónica experimental.
La intoxicación alumínica experimental produce una anemia microcítica con aumento de reticulocitos en sangre periférica. El hierro sérico y la capacidad de fijación de hierro de la transferrina no parecen modificarse.

SUMMARY

Aluminium-induced mycrocityc anaemia in experimental chronic renal failure.
Aluminium-intoxicated rats had a significantly lower haematocrit, haemoglobin and mean corpuscular volume than controls, and their reticulocyte count was increased. Serum iron and transferrin iron binding capacity were unchanged.

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Introduction

In chronic renal failure patients, the occurrence of microcytic anemia is most often due to an iron deficiency state. However, in a subgroup of hemodialysis patients with severe Al intoxication, the microcytic character of anemia may be much more pronounced than usually in iron deficiency [1-4]. Moreover, their serum ferritin is generally normal [3, 4]. The microcytic anemia remains unresponsive to iron supplements in such patients [1-3] but may be corrected by the interruption of Al intoxication using dialysis water deionization and reverse osmosis [1-4] as well as desferrioxamine treatment [5] and withdrawal of Al-containing phosphate binders [6].

However, the proof that Al was directly responsible for the sometimes severe microcytic anemia observed in Al-intoxicated hemodialysis patients, was only circumstantial. Therefore, we undertook the present experimental study in which chronically uremic rats were submitted to Al intoxication on a long-term basis [4].

Materials and methods

28 male Wistar AF rats were rendered chronically uremic by electro-cauterization of the renal cortex followed by contralateral nephrectomy one week later. Two weeks after nephrectomy, daily (6/7 days a week) intraperitoneal injections of Al sulfate (30 nmoles of elemental Al per day contained in 0.1 ml 0.9 % NaCl solution) were started in one half of the rats (n = 14). The other rats (n = 14; control animals) were allocated to an identical injection schedule with the vehicle solution only. The intoxicated and the control animals had comparable initial mean (± SEM) body weight (256 ± 3 and 264 ± 2 g, respectively) and plasma creatinine concentrations (107 ± 5.6 and 115 ± 13.2 µmol/l). At the end of the study, the animals were anesthetized with ether and exsanguinated by aortic puncture.

Analytical and statistical procedures

Plasma creatinine, iron, and iron binding capacity were determined using standard methods. Plasma aluminum determination was performed using graphite furnace flameless atomic absorption spectrometry [7]. The hematological parameters were measured by a Coulter counter (Coulter Electronics). Blood reticulocytes were counted in the usual way.

Statistical analysis of data was performed using Student's t test.

Results

The results of the initial hematological tests in group I (n = 14) and group II (n = 14) uremic rats were identical: 5.97 ± 0.22 vs 5.68 ± 0.21 × 10^6/mm^3 for RBC counts; 12.7 ± 0.5 vs 12.5 ± 0.5 g/dl for hemoglobin; 34 ± 1.3 vs 33.2 ± 1.1 % for hematocrit.

The hematological and biochemical data of group I (Al intoxicated) and group II (not intoxicated) rats obtained after three months of treatment are shown in table I. Mean RBC count, MCHC, serum iron, and serum creatinine concentration were similar in both groups of animals. However, mean hemoglobin and hematocrit were significantly depressed and reticulocyte count increased in Al intoxicated rats as compared to the control animals. Moreover, the mean MCV values were strikingly decreased after Al intoxication (Fig. 1). The mean plasma Al concentration of group I rats was significantly higher than that of control group II rats (table I).

Discussion

This experimental study has been the first to demonstrate that parenteral Al intoxication of chronically uremic rats led to a microcytic anemia. It thus confirmed the clinical suspicion of a cause-and-effect-relationship between this

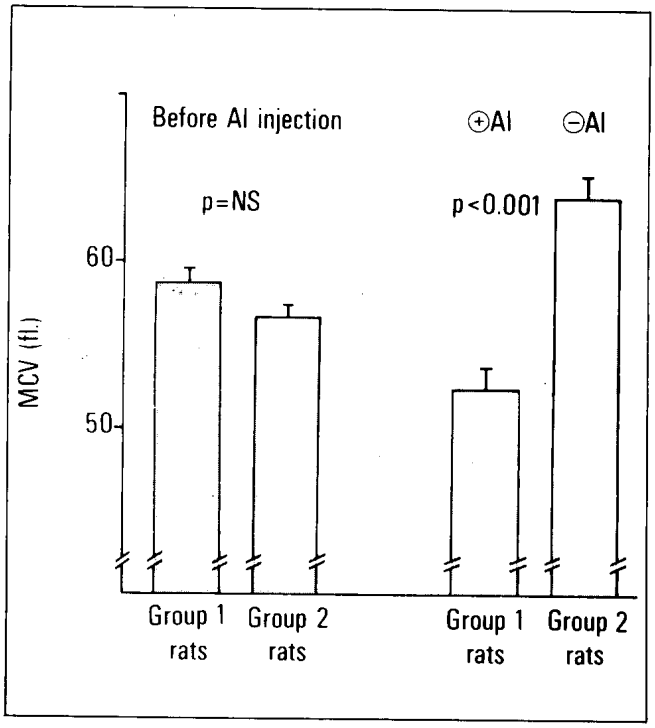

Fig. 1.—MCV results before and after aluminium (Al) injection.

Table I. Haematological and biochemical parameters after 3 months of IP injection in uraemic rats (means ± SEM)

	RBC ($\times 10^6$/mm^3)	Haemoglobin (g/dl)	Haematocrit (%)	MCHC (g/dl)	Reticulocytes ($\times 10^3$/mm^3)	Serum Iron (µmol/l)	Serum Creatinine (µmol/l)	Plasma Aluminium (µmol/l)
Group I + Al (n = 14)	6.71 ± 0.17	12.0 ± 0.20	34.7 ± 1.2	34.8 ± 0.9	161 ± 41	26.9 ± 1.8	225 ± 15.4	9.60 ± 1.10
Group II − Al (n = 14)	6.30 ± 0.13	13.1 ± 0.21	37.4 ± 1.8	34.9 ± 1.0	113 ± 21	30.4 ± 1.5	201 ± 10.3	0.69 ± 0.11
P	NS	< 0.001	< 0.001	NS	< 0.05	NS	NS	< 0.001

complication and the Al intoxication observed in hemodialysis patients [1-4]. In our study, uremic rats had already before the start of Al intoxication a slightly microcytic anemia which was due to chronic renal failure. The microcytic character of their anemia was however significantly aggravated after the Al injections during 3 months. Moreover, the anemia was slightly, although not markedly, worsened since hemoglobin and hematocrit decreased significantly. In a subsequent study in normal and uremic rats, Kaiser et al [8] confirmed our studies. However, whereas blood reticulocyte counts were increased in our Al-intoxicated rats as compared to controls, these authors found no change of circulating reticulocytes.

Different time course and Al injection modalities could, at least in part, be responsible for this discrepancy.

The precise mechanism by which Al causes anemia is unknown [9-11]. More studies are required in order to learn whether red cell production or destruction are modified. The possible intervention of toxic effects on delta aminolevulinic acid dehydratase activity [12] and on ferroxidase [13] requires still confirmation in experimental studies. Since recent experiments have shown that Al is bound to at least one of the specific iron-binding sites of transferrin [14], it is well possible that Al may interfere with pathways of iron distribution and metabolism.

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