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Occult lead intoxication as a cause of hypertension and renal failure

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Abstract

Background. The true incidence of lead (Pb) overload as a cause of chronic renal failure (CRF) is unknown. Also, it is unclear if CRF *per se* could generate an increment in the body Pb burden. Most studies of chronic Pb intoxication have been performed on cohorts or patients with a past history of occupational exposure. Therefore we studied the body Pb burden in CRF of known aetiology versus those patients with CRF with gout and hypertension of unclear aetiology without a past history of Pb exposure. In addition we studied patients diagnosed with essential hypertension.

Methods. We studied 296 patients lacking a past history of Pb exposure, who were subdivided into four groups: group I ($n=30$), normal control subjects; group II ($n=104$), patients with 'essential' hypertension and normal renal function; group III ($n=132$), patients with CRF of uncertain aetiology in association with hypertension and/or gout, and group IV ($n=30$), patients with CRF of known aetiology. The blood and urine Pb levels were assessed before and after an EDTA test.

Results. No abnormal test results were obtained for patients in groups I and IV. The EDTA test was abnormal in 16 patients (15.4%) in group II and in 74 patients (56.1%) in group III. A positive correlation was observed between plasma creatinine levels and post-EDTA urinary Pb in group III, but not in group I. No correlation regarding plasma creatinine and the duration of hypertension or gout were demonstrated. The bone Pb levels, measured in 12 patients with pathological EDTA test results, were positively correlated to the plasma creatinine levels.

Conclusions. A high percentage of patients with gout, hypertension, and CRF have an excessive Pb burden, and about 15% of the patients diagnosed as 'essential' hypertensives also show high Pb burdens. It is remarkable that a history of overt Pb exposure was lacking in the whole study population.

Key words: chronic renal failure; EDTA test; gout; hypertension; lead nephrotoxicity

Introduction

Lead (Pb) is classically considered to be an industrial hazard. Its long-term effects as an environmental pollutant and poison have only become a matter of concern in the last few years and is thought to be a world-wide risk for all populations. The idea of Pb-associated renal disease is an ancient concept [1], but still some degree of controversy persists even today as to the role of chronic Pb intoxication as a cause of chronic renal failure (CRF) [2–5]. Available reports, based in most cases on occupationally exposed workers [6–13], generally involve Pb as a cause of CRF, but still some do not find such a relationship [14,15]. It is even less clear whether Pb might be able to induce CRF in subjects with no known past history of long-term occupational exposure or acute intoxication. In other words, Pb may indeed be the cause of some cases of CRF of uncertain aetiology. Conversely, some reports pose the question whether CRF itself may be the cause of excessive Pb accumulation [4,5,16].

Chronic Pb intoxication may present with non-specific clinical signs or it may be subclinical. It can appear similar to progressive CRF associated with high blood pressure and gout with low-degree proteinuria [17]. Therefore, we investigated a large group of patients with this non-specific clinical presentation and without any history of previous occupational exposure to lead or acute intoxication. Blood and urinary Pb levels before and after an EDTA test, as well as bone Pb levels and porphyrin concentrations were determined.

Subjects and methods

The study population included 296 subjects, who were divided into four groups: group I ($n=30$), normal subjects; group II ($n=104$), patients with a diagnosis of essential hypertension

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and with normal renal function; group III ($n=132$), patients with CRF of uncertain aetiology in association with high blood pressure and/or gout. This group was further subdivided into two subgroups, III-A ($n=68$) with hypertension and CRF and with a presumptive diagnosis if nephroangiosclerosis, and III-B ($n=64$) with hypertension, gout and CRF. Finally, group IV ($n=30$) was composed of patients with CRF of known aetiology (chronic glomerulonephritis, adult polycystic kidney disease and chronic pyelonephritis). This latter group was included in order to rule out renal function impairment as the cause of excessive amounts of mobilizable Pb. The diagnosis of chronic glomerulonephritis was established through previous biopsies and adult polycystic kidney disease and chronic pyelonephritis were diagnosed with standard imaging procedures (ultrasound scan and radiology).

All the patients were residents of the same area of Madrid (Spain); most of them had completed their primary education and were in a low-medium income bracket.

Nephroangiosclerosis was presumed to be present in CRF patients with hypertension and low-level proteinuria (<1.5 g/24 h) when there was no clear aetiology and the radiological and ultrasound studies ruled out major arterial or urological disease. The diagnosis of essential hypertension was established when no specific cause for the observed high blood pressure could be detected. The severity of the hypertension was assessed by the presence or absence of left ventricular hypertrophy and/or fundoscopic changes. We also examined the previous medications used (diuretics and other antihypertensives) and the duration of known hypertensive disease. The blood pressure was measured at least every 6 months over 2 years.

The patients' records were carefully examined for indications of possible Pb exposure. Patients with a known current or past Pb exposure were excluded from the study. The alcohol and smoking habits were also assessed.

The stimulated Pb excretion was assessed according to Emmerson [17] with the modifications proposed by Batuman *et al.* [18]. The response to the chelating agent was measured as the summated urinary Pb excretion over the entire 72-h study period. It was postulated that the individuals with an abnormal Pb burden would excrete in excess of 600 μg/72 h of the metal [17,18].

Transiliac bone biopsy was performed in 17 patients.

The bone, blood and urinary Pb levels were measured by atomic absorption spectrometry (Perkin–Elmer Mod-5000, HGA-400 graphite furnace, AS-40 and Data System 3600) according to a method previously described by our group [19]. The blood samples were deproteinized with trichloroacetic acid and HNO_3 and the bone and urinary samples were treated with NO_3H. Matrix effect was avoided by the addition of ammonium molybdenum. The linearity reached 125 μg/l. The detection limit was 4 μg/l and the measurements remained linear until 125 μg/l. The recuperation values indicated an accuracy from 99 to 104% and the precision studied by Ringbom plots is from 9.2 (minor concentrations) to 1%. The blood Pb levels were corrected for the haematocrit. Bone lead determinations are expressed in μg/g of wet weight. The standard haematological and blood biochemistry parameters were assessed through autoanalyser evaluation.

The red blood cell delta-aminolaevulinic dehydrase activity was assessed as described by Berlin and Schaller [20], and the erythrocyte protoporphyrin levels were measured fluorometrically [21].

The results are expressed as means ±SEM. The statistical analysis procedures used were analyses of variance, Scheffe's test, Student's t test and single and multilinear regression analyses, as applicable. We used a statistical package for IBM PC (SPSS/PC).

Results

Pb determinations

Table 1 shows the renal function data, haematocrit, and Pb determinations for the four groups. The baseline urinary Pb levels were similar in all groups except group IV. The blood Pb levels were within normal ranges in all groups, but group III-B showed significantly higher levels than the other groups.

The EDTA test results were abnormal in 90 patients, all of them belonging to groups II or III. No abnormal results were obtained in group I or group IV (Table 2) and there were no significant differences in the post-EDTA urinary Pb excretion between these two groups, either when comparing the total Pb excretion over the 3 days or when assessing the daily Pb excretions. There were, however, differences in the baseline urinary Pb levels. In addition, no differences were found in the blood Pb levels between these groups.

A statistically significant correlation was observed between post-EDTA urinary Pb and serum creatinine ($r=0.45$; $P<0.001$; Figure 1a) only in the patients with

Table 1. Patient data for all groups

Group	Age (years)	CCr (ml/min)	Haematocrit (%)	Blood Pb(μg/dl)[a]	Urinary Pb[a]	
					Baseline (μg/24 h)	Post-EDTA (μg/72 h)
I	60.2±1.7	107.6±2.1[b]	42.0±0.6	16.7±1.5	68.1±5.7	324±21
II	53.5±1.4[c]	108.7±2.8[b]	42.6±0.4	16.8±0.4	56.5±2.7	487±45
III-A	59.6±1.8	46.6±2.2	41.2±5.2	18.5±0.5	67.3±7.3	678±80
III-B	59.5±1.3	41.4±3.7	40.4±0.8	21.1±1.0	65.4±10.9	1290±157[c]
IV	61.6±2.8	49.8±4.3	39.6±1.6	16.5±1.2	31.2±5.6[†]	321±28
P^d	0.026	0.0001	n.s.	0.001	n.s.	0.0001

Values are expressed as means±SEM.
[a] To convert values to μmol, multiply by 0.004826.
[b] $P<0.05$ versus group III-A, III-B and IV (Scheffe' test); [c] $P<0.05$ versus remaining groups (Scheffe' test).
[d] analyses of variance.

Table 2. EDTA test results

	Abnormal test			Normal test		
	n^a	Blood Pb (μg/dl)[b]	Urinary post-EDTA Pb (μg/72 h)[b]	n^a	Blood Pb (μg/dl)[b]	Urinary post-EDTA Pb (μg/72 h)[b]
G I	0	—	—	30 (100%)	16.7±1.5	324±21
G II	16 (15.4%)	18.2±1.2	1154±218[c]	88 (84.6%)	16.5±0.5	339±18[c]
G III A	30 (44.1%)	20.0±1.1	1177±135[c]	38 (52.9%)	17.2±0.9	283±14[c]
G III B	44 (68.7%)	21.7±1.3	1700±201[c]	20 (31.2%)	21.1±2.3	389±16[c]
B IV	0	—	—	30 (100%)	16.5±1.2	323±27

[a] n = Number of patients.
[b] To convert values to μmol, multiply by 0.004826.
[c] $P<0.01$ vs abnormal test results (Student's t test).

abnormal EDTA test results. No such correlation was seen in those with a normal EDTA test (Figure 1b).

The bone Pb levels were assessed in 12 patients with abnormal EDTA tests (Table 3). The mean value was 27.8±4.8 μg/g wet weight (0.134±0.023 μmol/g) vs 9.1±2.3 (0.044±0.011 μmol/g) in a control group of five healthy subjects. Again, a positive correlation (r = 0.595; $P<0.05$) was seen between bone Pb and serum creatinine in the patients with abnormal EDTA tests (Figure 1c) and between bone and post-EDTA urinary Pb excretion (r = 0.6, $P<0.05$).

The percentage of smokers was similar in the groups with normal and abnormal EDTA tests (23 and 26% respectively); high alcohol consumption (>30 g/day) was significantly more frequent in the patients with abnormal test results (29 vs 18% in those with normal results $P<0.05$).

Biochemical and haematological parameters

No basophilic stippling was seen with Wright's stain in the peripheral blood smears from patients with abnormal test results.

No deterioration of renal function was observed after the EDTA challenge.

The delta-aminolaevulinic dehydrase activity and the erythrocyte protoporphyrin levels were measured in 10 patients with pathological test results and in 25 with normal results and with comparable renal function. Only the delta-aminolaevulinic dehydrase levels showed statistically significant differences (11.3±2.2 versus 27.8±1.3 IU/ml; $P<0.001$).

Table 3. Lead levels in patients with abnormal EDTA test results

Blood Pb (μg/dl)	23.2±1.2
Bone Pb (μg/l)	27.8±4.8
Post-EDTA urinary Pb (μg/72 h)	2180±406
Urinary Pb 1st day post-EDTA test (μg/day)	970±125
Urinary Pb 2nd day post-EDTA test (μg/day)	811±193
Urinary Pb 3rd day post-EDTA test (μg/day)	399±156
Creatinine clearance (ml/min)	28.3±3.8

Patients with abnormal EDTA test and bone biopsy

Group II (hypertension with normal renal function)

Compared to those with normal EDTA test results, the patients in group II with abnormal EDTA test findings showed higher levels of proteinuria (0.129±0.03 versus 0.037±0.01 g/24h; $P<0.05$), higher serum uric acid levels (6.69±0.5 versus 5.60±0.1 mg/dl; $P<0.05$), and no differences in the endogenous creatinine clearance (108±4.5 versus 109±3.6 ml/min). The hyperuricaemia was not associated with diuretic use. The severity of the hypertensive disease was similar in both patient subgroups, as assessed by the degree of blood pressure control, electrocardiography, retinal changes, and number of antihypertensive drugs required (2.0±0.4 versus 1.7±0.14).

Group III-A (chronic renal failure with hypertension, but without gout)

The subgroup with abnormal EDTA test results had higher serum uric acid levels (7.9±0.3 versus 6.4±0.2 mg/dl or 0.469±0.017 versus 0.380±0.011 mmol/l; $P<0.05$); no patient in the group had previous episodes of gouty arthritis. The creatinine clearance was lower in patients with excess Pb (38.0±2.5 vs 54.4±3.1 ml/min; $P<0.001$) and the degree of proteinuria was similar for both subgroups (0.65±0.15 versus 0.51±0.16 g/24 h). The percentage of patients on diuretics was 27 and 42% in the subgroups with abnormal and normal test results respectively. The differences in the remaining biochemical and haematological parameters, and the severity of hypertension were not statistically significant between the subgroups. The duration of known hypertensive disease was also similar in both subgroups 12.02±2.1 versus 10.5±1.3 years. No correlation was detected between the serum creatinine levels and the duration of known hypertensive disease.

Group III-B (chronic renal failure with hypertension and gout)

Hyperuricaemia and gout were present in all cases in this group prior to the diagnosis of CRF. The patients

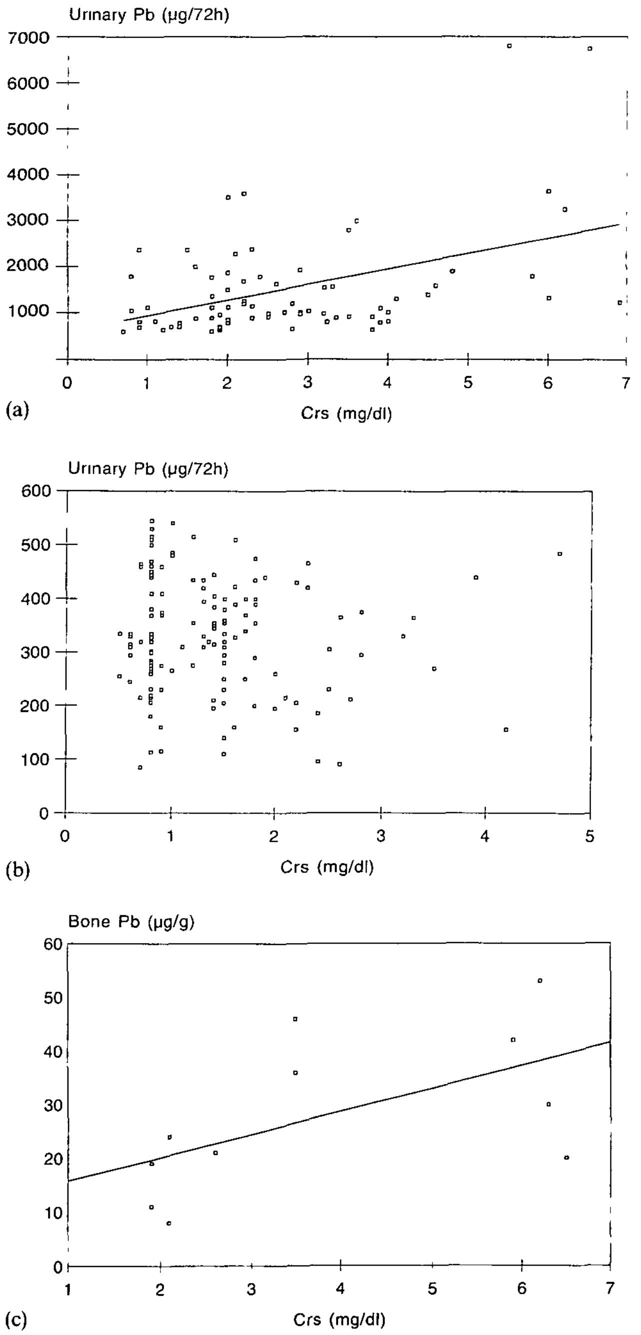

Fig. 1a. Relationship between serum creatinine and post-EDTA urinary Pb in patients with abnormal test results. $y = 613.8 + 334.8\,x$ ($r = 0.45$; $P < 0.001$). To convert values for creatinine to μmol/l, multiply by 88.4; to convert values for lead bone to μmol, multiply by 0.004826.
Fig. 1b. Relationship between serum creatinine and post-EDTA urinary Pb in patients with normal test results ($r = -0.05$, $P = $ns). To convert values for creatinine to μmol/l, multiply by 88.4; to convert values for lead bone to μmol, multiply by 0.004826.
Fig. 1c. Relationship between serum creatinine and bone lead levels in 12 patients with pathological EDTA test. To convert values for creatinine to μmol/l, multiply by 88.4; to convert values for lead bone to μmol, multiply by 0.004826.

with abnormal EDTA test results had lower creatinine clearances than those with normal Pb loads (38.3 ± 5.3 versus 56.4 ± 7.6 ml/min; $P < 0.01$). There were no statistically significant differences between the two subgroups in the proteinuria levels (0.76 ± 0.1 versus 0.6 ± 0.2 g/24 h respectively) nor in the remaining biochemical or haematological parameters or the severity of the hypertension. The durations of known hypertensive disease (12.0 ± 1.9 versus 10.3 ± 2.4 years) and of known hyperuricaemia (11.2 ± 2.5 versus 12.2 ± 3.8 years) were also similar. A positive correlation was found between serum creatinine and post-EDTA urinary Pb ($r = 0.575$; $P < 0.01$) in this group. The linear correlation analyses revealed that there was no correlation between serum creatinine and duration of known hypertension, nor between serum creatinine and the duration of known hyperuricaemia.

Discussion

There are still a number of unanswered questions regarding Pb nephrotoxicity. The present study was designed to answer two questions: (1) is there Pb retention in CRF, and (2) even in the absence of previous overt Pb exposure, how many patients with CRF of unknown aetiology have an excessive Pb burden as the possible cause for their renal disease?

To elucidate whether Pb is retained in CRF it is imperative to establish two control groups, one with normal renal function and the other with CRF of known cause. To try to find an answer to the second question it is important to compare a group of patients with CRF of known cause with a group of patients with CRF of unknown aetiology, but with clinical features suggestive of chronic Pb nephropathy. It would be useless to compare only healthy controls and 'CRF patients' as the latter would represent a mixture of patients with CRF of known and unknown aetiologies, all of them with or without overt Pb exposure. With the study designs used by a number of authors [4,5,22–24] it is only possible to state that some CRF patients have high levels of Pb burden, but it is impossible to clearly discern what proportion of CRF is a consequence of the excessive Pb burden.

Our data suggest that CRF does not in itself lead to Pb accumulation because the excretion of chelatable Pb was the same in the healthy controls and the CRF controls, which is in agreement with other reports [16–18, 25]. On the other hand our group III (chronic renal failure of unknown aetiology with hypertension and hyperuricaemia) contained a very high proportion of patients with abnormal post-EDTA Pb excretion. We and other investigators [18,25] have found a direct correlation to exist between severity of CRF and chelatable Pb excretion (Figure 1a). The baseline blood Pb levels in the patients in our group III were high. From these data we might infer, in agreement with Batuman [18], that the greater the accumulation of Pb, the greater the excretion, and that greater accumulation induces more severe CRF. It cannot be ruled out, however, that EDTA may be retained in CRF because it is only excreted by glomerular filtration [26], leading to a greater amount of bone Pb being chelated by it [17]. Our data do not support this hypothesis because a direct relationship between serum creatinine and excreted Pb was not maintained in patients with normal tests (Figure 1b). To our knowledge, we are the first to report a clear relationship between bone Pb content and GFR in patients with a pathological EDTA test (Figure 1c). This finding clearly establishes a relationship between the degree of Pb accumulation and the severity of the nephropathy. It appears reasonable to assume that the levels of Pb excreted after the chelation test reflect the Pb burden, and that higher intoxication levels are associated with more severe nephropathy.

Staessen *et al.* [24] recently reported an inverse correlation between the creatinine clearance and the blood Pb levels in a study involving a random population of 1981 individuals with normal and impaired renal function. Unfortunately blood Pb levels are not a suitable basis for the diagnosis of chronic Pb intoxication as they are only an indicator of recent exposure. There is no doubt that the EDTA test has a much greater diagnostic value than blood Pb levels, and yet there have only been a few studies using this test [18, 27] in subjects without overt history of Pb exposure. Furthermore the Staessen study does not state the aetiology of the CRF, nor do they address the question of whether there is an accumulation of Pb in CRF. In addition they do not investigate the possible causative role of Pb overload in CRF, thus precluding any comparison of their data with ours.

The inclusion of a study group similar to our group III (CRF with hypertension and hyperuricaemia) is frequently absent in reports in the literature. Many studies contain groups of patients with mixed aetiologies of CRF, or groups of patients with and without previous history of Pb exposure. Sometimes patients are selected based on a history of gout, eventhough primary gout is an entity in which the prevalence of Pb accumulation is not high, thus rendering those studies open to criticism. Our group III was selected on the basis of clinical features comparable to those described in chronic Pb intoxication [17]. This clinical similarity, together with the high blood and bone Pb levels and the high post-EDTA urinary Pb excretion render it tempting to group all these findings together as a single and unique disease entity which may be associated with the high bone Pb levels reported in dialysis patients [16].

Several publications by Ritz's group have reported high percentage of cases with elevated corporal Pb burdens in CRF of varying aetiologies [4,5]. Many of these patients had past histories of Pb exposure, and the authors did not distinguish between CRF patients with clinical features comparable to those of chronic renal saturnism and those without. They conclude that high corporal Pb burdens might precipitate a previously present CRF. However, this assertion is not supported by clinical data, but rather by those of an experimental model [28] of partially nephrectomized rats with or without Pb exposure. Their conclusion may be valid, but these studies do not provide an answer to the very important question regarding Pb as a unique cause of CRF.

In our study, 15% of the patient population ($n=104$) with a diagnosis of essential hypertension had abnormally high corporeal Pb burdens. These patients must be considered to constitute a more 'difficult' population of essential hypertensives, as they had been referred to our hospital for assessment. Considering our results, we estimate that a certain proportion of the supposedly 'essential' hypertensives might well represent cases of chronic Pb intoxication, and that this might explain a certain proportion of those 'essential' hypertensives who develop CRF despite good blood pressure control and follow-up of their hypertension [29].

In agreement with the findings of others [16] we conclude that Pb is not accumulated in CRF. A very high percentage of CRF patients with clinical features of nephroangiosclerosis and gout have high corporeal Pb burden levels in the absence of prior overt Pb exposure. A direct relation exists between CRF and post-EDTA excreted Pb and between CRF and bone Pb content only in patients with abnormal EDTA test results. These data suggest that CRF does not lead to Pb accumulation by itself. If CRF patients exist who have a distinct and definite clinical picture resembling chronic occupational or childhood Pb poisoning and high levels of corporeal Pb burden, then it is reasonable to think that Pb is the cause of the CRF in those patients (group III with his Pb burdens), even though the source of Pb exposure remains unclear.

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