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SERUM TRACE ELEMENTS IN HEMOPROLIFERATIVE DISEASES.

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Abstract

The PIXE method has been used to compare a reference group (N=100) and eight groups of patients suffering from hematological malignancies (Hodgkin's disease, lymphosarcoma, chronic lymphocytic leukemia, acute lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, myeloproliferative disorders and myeloma) (N=140).
The serum Cl, K, Ca, Fe, Cu, Zn, Se and Br contents have been measured. Significative differences were noted in several groups. A statistical analysis has been performed to correlate these trace element values with several clinical and biological parameters such as blood cells counting, clinical stage, histology, inflammatory tests,...

Introduction

Trace elements metabolism has already been extensively studied in various medical fields (1, 2). In hematology, many authors have reported on serum copper increase in Hodgkin's disease and lymphosarcoma and return to normal values when complete remission is achieved (3, 4, 5, 6). Much less has been described about other trace elements, especially about bromine whose role in human metabolism remains obscure.
We report here on our experience with serum trace elements dosage and confirm our previous communication (7) on abnormal values in several hemoproliferative diseases.

Patients and methods

The PIXE method has been used to measure the serum content of chlorine (Cl), potassium (K), calcium (Ca), iron (Fe), copper (Cu), zinc (Zn), selenium (Se) and bromine (Br), in normal subjects and in patients suffering from hemoproliferative diseases.

1) Normal subjects. This group was composed of 100 healthy subjects taking no drug. Although this group was rather younger than our patient group, no significant difference with age was noted in trace element values. We found a statistically significant difference between sexes in calcium (103 in male versus 100 ug/ml in female, $p = 0.03$), copper (1.05 in male versus 1.17 ug/ml in female, $p = 0.02$), zinc (1.14 in male versus 1.01 ug/ml in female, $p < 0.001$).
2) Patients. 319 samples were taken from 150 patients, many of them being studied on several occasions, both in active disease and in remission. They are divided up as follows : myeloma (MY : 20), Hodgkin's disease (HD : 12), lymphosarcoma (LS : 28), chronic lymphocytic leukemia (CLL : 26), acute lymphocytic leukemia (ALL : 6), acute myelocytic leukemia (AML : 26), chronic myelocytic leukemia (CML : 11) and myeloproliferative disorders (MPS : 21).
   We also studied serum trace elements values according to clinical status and some biological parameters usually regarded as representative of disease activity. So blood cell counting, erythrocyte, sedimentation rate, fibrinogen, serum lactate deshydrogenase (LDH) and serum proteins were recorded on the same day as the trace elements.
   Thirteen patients presenting with newly diagnosed or relapsing AML and undergoing intensive induction chemotherapy, have been serially followed for up to three months. The chemotherapy regimen generally consisted in a seven-day course associating high doses of daunomycine, vincristine and cytosine-arabinoside. Samples were taken before treatment and then about twice a week.

Table 1 - Serum copper, zinc and bromine (ug/ml) in controls and different patient groups. P-value for Student t-test is given when significant.

TABLE 1.

	COPPER	ZINC	BROMINE
N (100)	1.10	1.10	5.36
AML (26)	1.34 ($P < 0.001$)	0.94 ($P < 0.001$)	4.00 ($P < 0.001$)
LS (28)	1.40 ($P < 0.001$)	0.82 ($P < 0.001$)	4.70 (NS)
CLL (26)	1.65 ($P < 0.001$)	0.96 ($P < 0.001$)	4.10 ($P < 0.005$)
CML (11)	1.26 ($P < 0.05$)	0.99 ($P < 0.05$)	4.80 (NS)
MPS (21)	1.34 ($P < 0.001$)	1.00 ($P < 0.01$)	7.10 (NS)
HD (12)	1.34 ($P < 0.002$)	0.83 ($P < 0.001$)	6.17 (NS)
MY (20)	1.29 ($P < 0.005$)	0.87 ($P < 0.001$)	4.13 ($P < 0.002$)
ALL (6)	1.18 (NS)	0.88 ($P < 0.002$)	4.81 (NS)

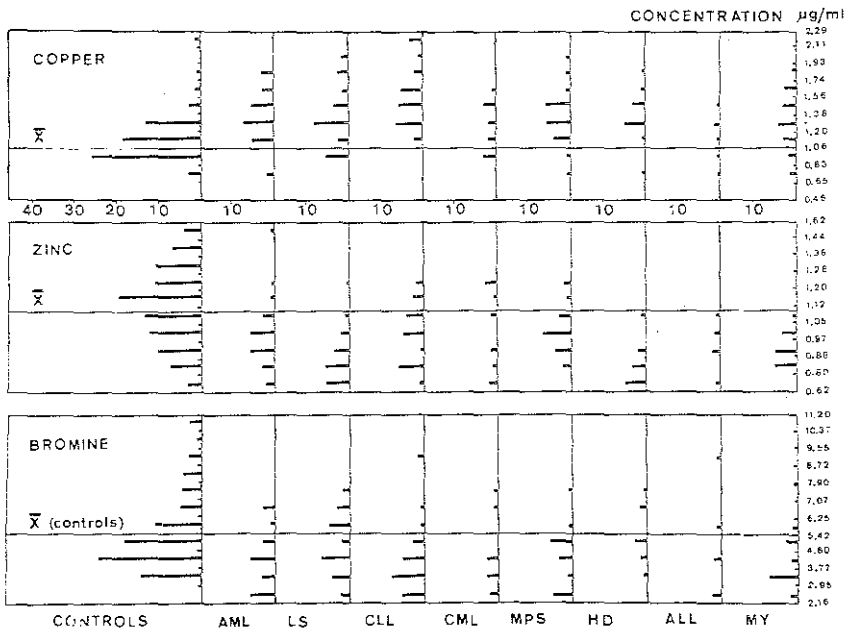

Fig. 1 - Serum copper, zinc and bromine (ug/ml) in controls and different patient groups, with range demonstrated.

Results

The mean values for copper, zinc and bromine in normal subjects and in patients are listed in Table 1. P-values for student t-test between controls and patients are mentioned when significant. Ranges are shown in Figure 1, but some very high values for bromine are outside this picture.

Copper was always increased when compared with controls, and this reached statistical significance in all groups but ALL which was too small. Zinc was significantly reduced in all patient groups, though the absolute difference wasn't important in every groups.

Bromine displayed some less systematic pattern. It was significantly decreased in AML, CLL and myeloma, but in AML this feature is dependent upon treatment (see below); it was slightly reduced in lymphosarcoma, CML and ALL, and slightly enhanced in HD and MPS, but in these groups most values were in fact very low and the mean artificially normalised by very high values.

Selenium showed no difference neither in absolute value nor in range.

Chlorine and calcium remained almost constant from group to group. Potassium was often increased, reflecting extensive cellular turn-over. Iron was sometimes reduced, mostly in CLL and LS groups where copper reached the highest levels.

Because of the small size of some groups, one must be careful in interpreting apparent correlations between trace elements and biological parameters. So we shall report only on the most important ones. Within the patient group as a whole, copper is correlated with white blood cell counts, inflammatory tests, serum LDH and potassium; zinc disclosed a weak correlation with calcium, iron and selenium, and bromine with potassium; potassium was related to whole blood cell counts, serum proteins and chlorine; calcium increased with serum proteins, chlorine, potassium and selenium.

In CLL, copper was correlated with WBC counts ($R=0.71$, $p < 0.001$), serum LDH ($R=0.796$, $p < 0.001$), ESR ($R=0.504$, $p < 0.05$) but not with fibrinogen; on the opposite, selenium was inversely correlated with WBC counts ($p < 0,01$). In lymphosarcoma, copper showed significant correlation with

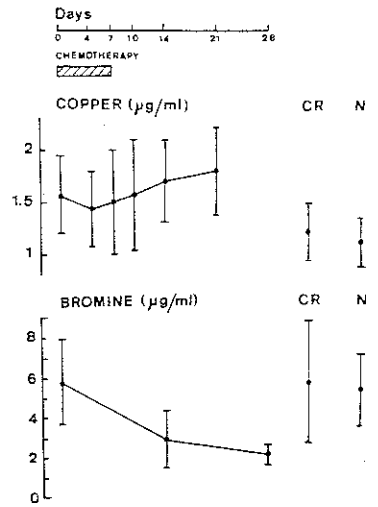

Fig. 2 - Copper and bromine evolution in patients undergoing chemotherapy for AML? Mean values $\pm$ σ are given with comparison with AML in complete remission (CR) and normal controls (N).

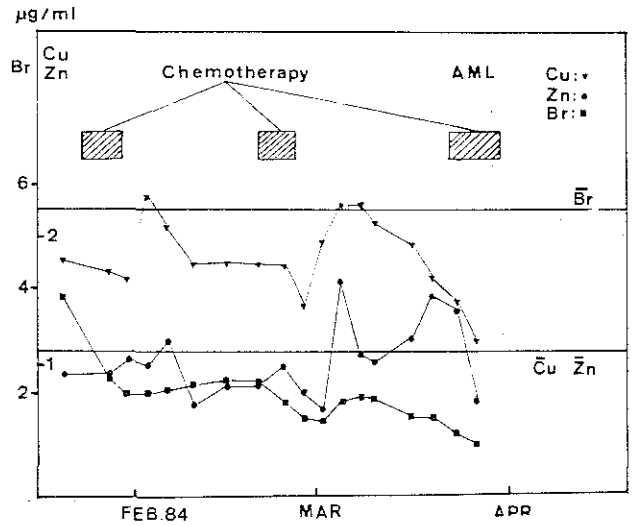

Fig. 3 - A typical pattern of bromine, copper and zinc evolution during chemotherapy in a 20 year old woman with AML.

ESR and fibrinogen, and inverse relationship with hemoglobin.
The AML patients undergoing intensive chemotherapy bore a characteristic evolution (Figure 2). The mean values before treatment were 5.79 ± 2.07 ug/ml for bromine and 1.57 ± 0.37 ug/ml for copper. Bromine dropped dramatically to 2.74 ± 1.45 on day 14 and 2.10 ± 0.48 ug/ml on day 28; the level remained low for several weeks and then progressively reached normal pre-treatment values. Copper displayed a less constant pattern but usually cut down during chemotherapy and thereafter reaugmented to significantly a higher level (1.79 ± 0.43 ug/ml on day 21). A few weeks later, while in complete remission, dosage reduced to 1.21 ± 0.28 ug/ml, thus only slightly more than in controls. A typical pattern is presented in Figure 3 with a 20 year old woman undergoing three chemotherapy courses for refractory AML.

Conclusions

1) Zinc is systematically reduced in hemoproliferative diseases. This has not always been confirmed (8) and doesn't seem to be related to nutrition status, treatment or other biological abnormalies. It may be due to tissular catabolism in cancer patients (1, 2).
2) Copper is usually enhanced in our patients but considerable overlap with normal values prevents us from its excessive clinical use. Nonetheless, we found a significant correlation between copper, and inflammatory tests in LS (3-6), and WBC chiefly in CLL.
3) Bromine remains misunderstood in human metabolism. Although we observed a general tendency towards decreased values in patients, very high values were noted, that were not related to any peculiar disease status nor to drug intake. The fall noticed in AML chemotherapy was independent of digestive tolerance to disease and treatment. This was supported by the absence of such a phenomenon in patients undergoing a slimming fast (unpublished data). This drop seemed to be due to chemotherapy itself.
4) Selenium is much the same in our patient groups as in controls. But measured concentration is very low and errors may be relevant.

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