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CHANGES IN SERUM ELEMENTS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA BEFORE AND DURING THERAPY*

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In most cases of acute lymphoblastic leukemia (ALL) a rise in the serum copper (Cu) level has been observed and a lowering of the serum Cu level during therapy is normally regarded as a sign of the effectiveness of the therapy[1-4]. In some patients quantitative variations from the normal of other serum elements such as Ca (calcium), P (phosphorus), K (potassium) and Na (sodium), have been observed before and during therapy[1]. The mechanisms of these changes before therapy are usually explained on the basis of infiltration of some organs by leukemic cells causing tissue damage or an increased turnover of the leukemic cell itself[1].

In the case of hypercalcemia, an increased production of parathyroid hormone (PTH), due to leukemic infiltration of the parathyroid glands or production of a PTH-like substance by leukemic cells has been suggested[5-7]. The changes pertaining to the elements during therapy have been explained on the basis of increased damage to the leukemic cells causing a transitional functional renal failure and of the direct effects of the cytotoxic drug on the endocrine glands similar to that observed in inappropriate antidiuretic hormone (ADH) secretion[8-10].

We studied our patients with ALL to evaluate: a) the frequency and the type of abnormalities in the serum elements, b) the relation between these abnormalities and the clinical and hematological findings and c) whether changes in the level of the serum elements during therapy would indicate the efficacy of the treatment.

Material and Methods

Nineteen patients with ALL aged between 2.5 and 16 years are the subjects of this study. Diagnosis of ALL was made by morphological examination of the bone marrow in all patients.

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Routine hematological studies were performed by standard methods. Bone marrow smears were obtained by needle aspiration biopsy[11]. Serum Cu, Zn, and Mg were determined by atomic absorption methods[12]. Serum Ca, P, Na, K and uric acid were determined by conventional procedures[13]. Blood was drawn before the commencement of any therapy and 12 hours later and thereafter every day up to the sixteenth day of therapy. X-rays for bone survey and chest X-rays were taken of all patients before commencement of therapy. Intravenous pyelography was performed in Case 1 for evaluation of palpable kidneys apparent on physical examination.

Results

The clinical and hematological findings are shown in Table I and levels of serum elements before therapy are shown in Table II. Before therapy, the mean serum Cu level vas significantly higher in patients than in controls (254 ± 53 and 148 ± 30 mg/dl respectively). There were no significant differences between the mean values of Zn, Mg, Ca, P, Na and K of the patients before therapy and those of the controls. There were also no statistically significant differences between the means of Zn, Mg, Ca, P, Na and K before therapy or on any day during the therapy. Severe hypercalcemia (serum Ca $\geqslant$ 12.5 mg/dl) was observed in four and hypocalcemia (serumCa$\leqslant$8.5 mg/dl) in two patients before therapy. There were no significant correlations between the white blood cell count, Hb level and serum elements before therapy. The changes in serum Ca, Cu, Zn and Mg levels are shown in Figures 1-4. The frequencies of abnormalities in serum element levels are shown in Table III.

Discussion

Hypercalcemia is reported to be present in 2.5% of all leukemic patients[1]. In our study hypercalcemia was present in 21% and hypocalcemia in 5% of patients before therapy. The discrepancy between these figures is quite striking. We believe that the values given in the literature reflect the result of a non-random selection, and more study is needed to obtain reliable figures.

The presence of bone infiltration in Case 1 (Tables I and II) suggested that this might be a cause of the hypercalcemia observed in this patient as has been reported previously[8]. The presence of renal infiltration in the same patient is interesting; however, it is necessary to investigate the serum Ca level in further patients with leukemic kidney infiltration before coming to any conclusion about a correlation between hypercalcemia and such infiltration. The possibility of the production of a PTH-like hormone by leukemic cells in patients with hypercalcemia has been suggested[14]. However, an elevation of the PTH level has not always been shown in these patients. The presence of a PTH immunologically different from the normal was suggested, but this subject needs to be further clarified[15]. Hypercalcemia has

TABLE I

Clinical and Hematological Data

Patient No.	Age (years), sex	First WBC 10^9/L	Hb g/dl	Liver cm	Spleen cm	Organ infiltration
1	2.5 M	13.6	11.0	–	–	Bone, kidney
2	3 F	5.4	6.1	3	–	–
3	3.5 F	250.0	7.1	6	6	Bone
4	4 M	16.6	5.4	3	3	Bone
5	5 M	110.0	8.5	10	10	Mediastinum, bone
6	5 M	15.3	7.98	4	–	–
7	6 F	6.8	13.1	2	–	–
8	5 M	3.6	4.7	4	9	–
9	6 M	9.6	9.5	7	6	–
10	7 M	18.4	9.8	3	4	–
11	8 F	31.2	9.4	7	8	Mediastinal mass
12	12 F	1.6	8.6	–	–	–
13	15 F	1.5	4.7	–	–	–
14	5 M	8.8	9.5	10	4	–
15	2 M	12.0	4.8	4	7	–
16	2 M	5.0	5.0	4	–	–
17	4 M	14.0	8.9	4	2	Mediastinal mass
18	11 M	100.0	11.0	6	3	–
19	13 M	38.0	6.0	9	5	–
Mean ± SD	6.26 ± 3.8	39.02 ± 61.4	7.95 ± 2.5	5.4 ± 2.5	5.5 ± 2.5	

TABLE II

Serum Elements before Therapy

Patients	Uric acid mg/dl	Ca mg/dl	P mg/dl	Cu µg/dl	Zn µg/dl	Na mEq/ L	Cu/Zn	K mEq/L	Mg mg/dl
1	13.3	18.3	5.4	–	–	135	–	3.6	–
2	6.8	10.3	4.6	328	96	152	3.42	5.1	3.08
3	10.0	9.5	–	296	62	–	4.77	4.5	3.0
4	10.5	8.5	7.5	276	60	141	4.60	3.6	2.28
5	5.0	9.5	5.0	340	96	143	3.54	4.5	2.52
6	3.6	7.5	4.4	220	40	150	5.50	3.4	1.80
7	6.4	11.0	5.5	216	76	145	2.84	4.4	2.40
8	6.8	11.5	6.6	328	60	147	5.47	3.7	1.72
9	17.2	10.0	5.6	180	68	140	2.65	3.8	2.24
10	7.1	9.0	4.8	256	84	136	3.05	3.7	2.08
11	8.0	9.8	–	284	76	145	3.74	3.6	2.40
12	4.3	9.3	4.6	196	80	149	2.45	4.2	2.52
13	13.9	9.0	5.2	292	64	–	4.56	4.4	2.40
14	–	14.8	4.5	225	121	–	1.86	–	–
15	–	10	5.4	145	148	–	0.98	–	–
16	–	15	3.6	217	–	–	–	–	–
17	–	12	6.2	258	125	–	2.06	–	–
18	–	11.4	5.0	261	130	–	2.01	–	–
19	–	9.4	4.1	226	144	–	1.57	–	–
Mean ± SD	8.7 ± 4	10.83 ± 2.64	5.29 ± 1.18	254 ± 53	90 ± 32.51	143.9 ± 5.5	3.24 ± 1.37	4.0 ± 0.51	2.37 ± 0.4
Range of normal	7	9-11*	4-6	65-145	40-140	135-150	0.98-2.42	3.5-5.5	1.8-3.0

* Hypercalcemia was considered to be present when the level of serum Ca ≥ 12.5 mg/dl and hypocalcemia when the level of serum Ca ≤ 8.5 mg/dl.

been reported to be present in ALL of the T-cell type[16]. We have not performed immunological typing in our patients. However, some of the expected signs of T-cell leukemia, such as an increase in the number of white blood cells and in the hilar mass, are absent. Hypocalcemia was observed in two patients prior to therapy and in four patients 12 hours after therapy had commenced; the concomitant serum P level was high in the patient with a serum calcium level of 5.8 mg/dl and it was normal in the other three, including the one with a calcium level of 4.8% mg/dl. Transient hypocalcemia was observed in several patients up to the termination of therapy (Figure 1). Although it had been suggested that the drop in the serum calcium level after the commencement of therapy is always accompanied by a change in the serum P level[9], the serum P level was always within normal limits in our patients. The conditions of hypoproteinemia and calciuria which may be resultant on therapy, need to be evaluated in further patients. Hypocalcemia was found to be transient and did not continue for more than two days in any patient.

Our study supports previous observations that the serum Cu level is usually elevated in the patient with leukemia before therapy and is a good marker in monitoring the effectiveness of the therapy. A significant fall was observed as early as on the second day of an efficient therapy (Figure 2).

Hypomagnesemia was observed in only a few patients (Figure 4), and the cause of this needs to be evaluated in more patients who could be followed prospectively.

Although the mean Zn level of the patients was not significantly different from the normal on any given day of therapy, there were quite a few patients (Figure 3) with hypozincemia, which is an expected finding among patients with hypercupremia. However, no significant correlation was present between the serum Cu and Zn levels. The Cu/Zn ratio in patients before therapy was significantly higher than in the controls, which is more likely to reflect an increased Cu level than a decreased Zn level.

During therapy a rise in the serum K level was reported in some patients. This was due to transitional renal tubular failure caused by increased nucleoprotein catabolism[1,9].

Hyponatremia has been noted in a few patients sometimes in a manner related to the above stated mechanism, or in connection with inappropriate ADH secretion due to vincristine administration[10]. Our study did not disclose any abnormalities in the Na and K levels, thus indicating that among the elements examined in this study these two electrolytes are the least influenced by leukemia or cytotoxic therapy.

In conclusion we would like to suggest the importance of determining the serum Ca level in patients with leukemia before and during therapy since significant changes may occur. The importance of trials of specific treatment for hyper- or hypocalcemia needs to be further studied.

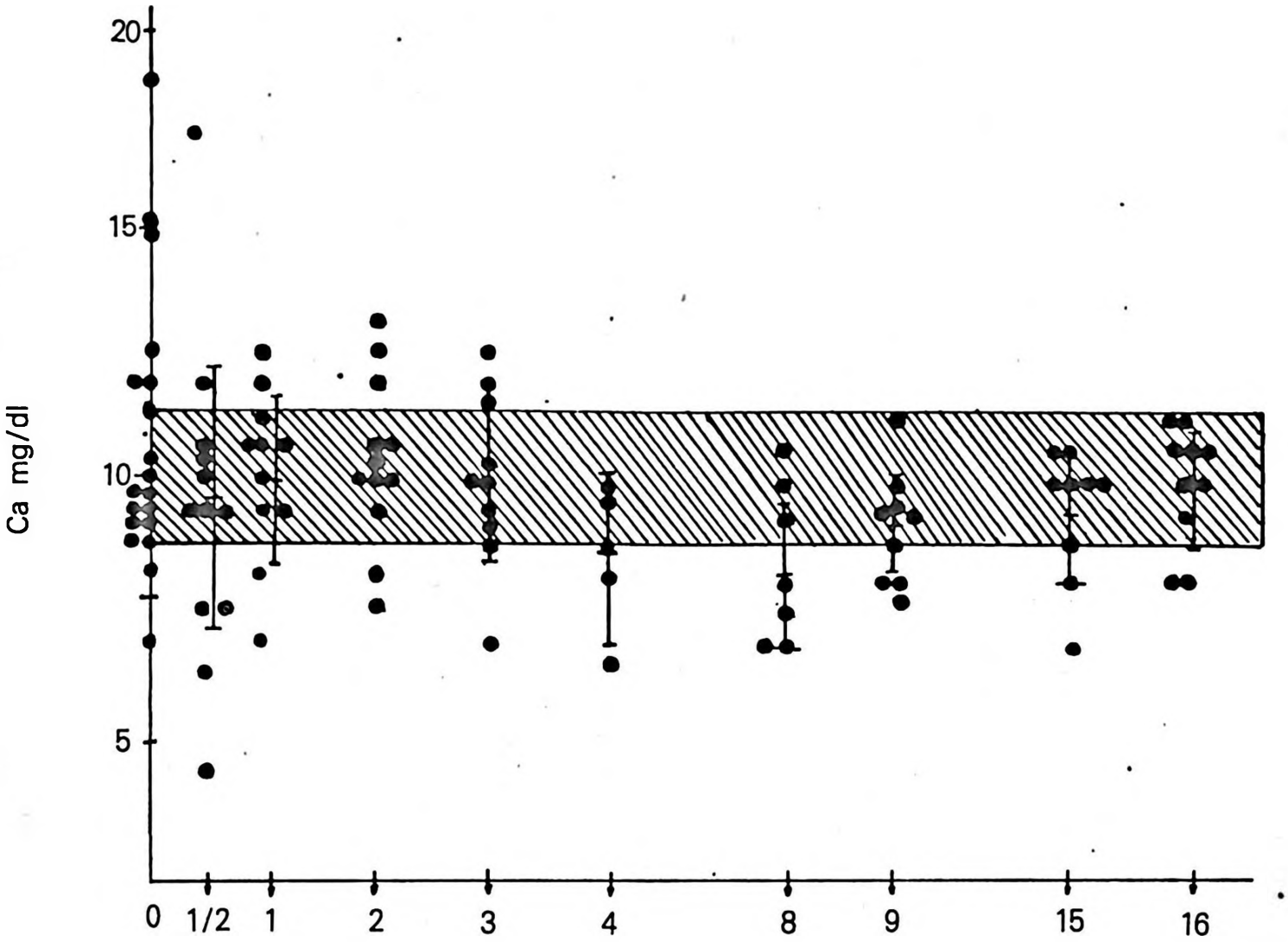

Figure 1.

The numbers on the horizontal axis indicate time in days. Vertical lines indicate the mean ± SD for a given day. The hatched area represents normal values. Serum hypercalcemia was diagnosed when serum Ca ⩾ 12.5 mg/dl and hypocalcemia when serum Ca ⩽ 8.5 mg/dl.

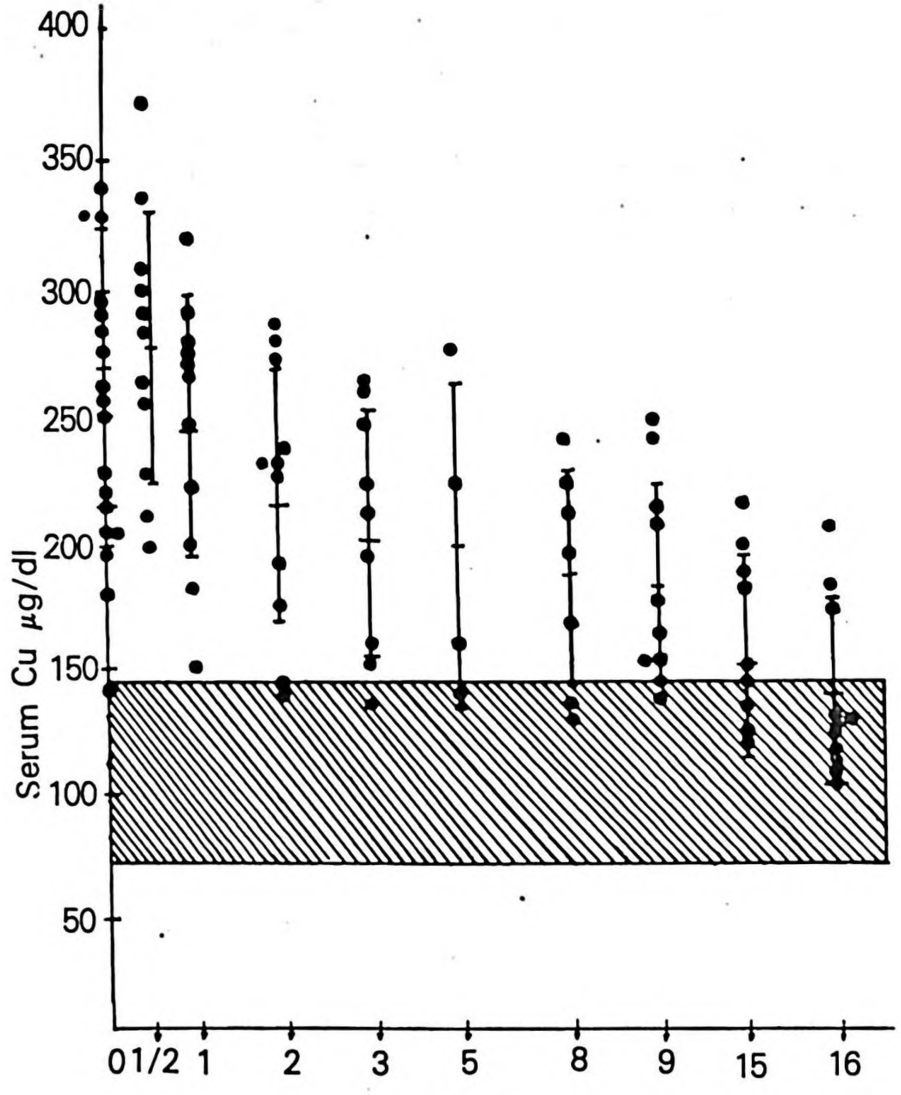

Figure 2.

The numbers on the horizontal axis indicate time in days. Vertical lines indicate the mean ± SD for a given day. The hatched area represents normal values.

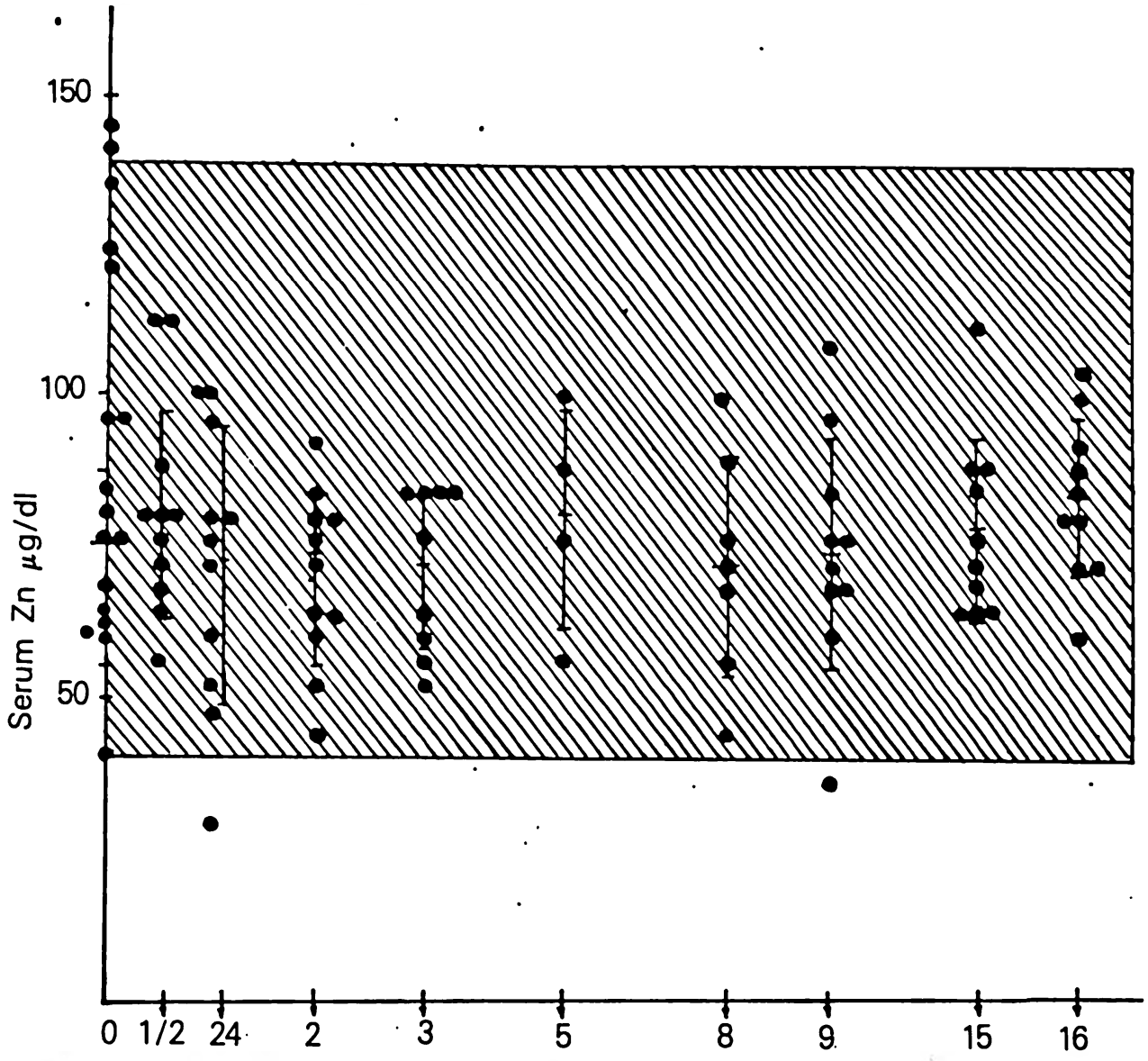

Figure 3.

The numbers on the horizontal axis indicate time in days. Vertical lines indicate the mean ± SD for a given day. The hatched area represents normal values.

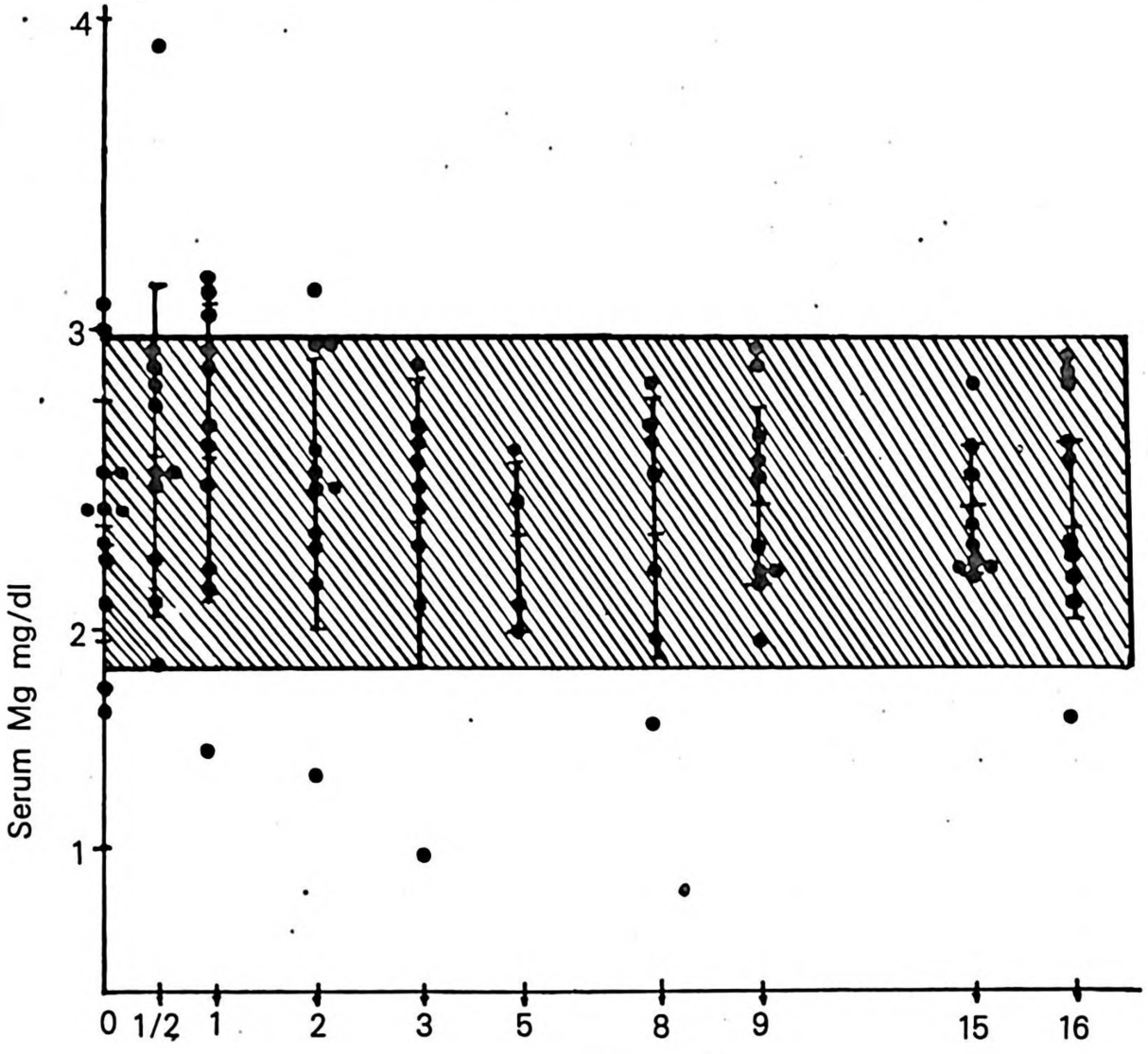

Figure 4.

The numbers on the horizontal axis indicate time in days. Vertical lines indicate the mean ± SD for a given day. The hatched area represents normal values.

TABLE III

Percentage Frequencies of Abnormal Serum Element and Uric Acid Levels in Patients before Therapy

Increased Cu	Decreased Zn	Increased Cu/Zn	Increased Ca	Decreased P	Increased P	Increased Uric Acid
95% (17/18)*	24% (6/17)	66% (12/18)	21% (4/19)	5% (1/19)	12% (2/17)	46% (6/13)

* Figures in parentheses show number of patients with abnormal values and total number of patients whose values were determined.

Hypercupremia is to be expected prior to therapy, and a close follow up of the serum Cu level might be useful in monitoring the effectiveness of the therapy.

Although the mean of the serum uric acid level is significantly higher in patients with leukemia than in the controls, no significant correlation was found between the uric acid level and any other parameters studied, indicating that increased nucleoprotein catabolism is not the only mechanism responsible for the changes in some of the serum elements in ALL.

Summary

Some of the trace elements, electrolytes, serum Ca, P and uric acid levels were measured in 19 patients with acute lymphoblastic leukemia before commencement of therapy, after 12 and again after 24 hours and thereafter every day up to the 16th day of the therapy.

The elevation of the mean serum Cu in patients compared to normal control levels was found to be statistically significant ($p < 0.001$, 254 ± 53 and 148 ± 30 mg/dl; respectively). The serum Cu level began noticeably to fall to the normal level 24 hours after the commencement of therapy. Before therapy hypercalcemia and hypocalcemia were observed in 21% and 5% of patients respectively. A transient hypocalcemia developed in a few patients in the course of therapy.

There were no statistical differences in serum Zn, Ma, K and P levels between patients and controls.

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