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Serum iron level in acute lymphoblastic leukaemia

By

L. LEGUTKO

Second Department of Paediatrics, Medical Academy, Cracow—Prokocim, Poland

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Serum iron level (SIL) was studied by atomicabs orption spectrophotometry in 57 children with acute lymphoblastic leukaemia. SIL depended on the activity of the disease. Mean SIL was highest in untreated children. Normalization of myelograms during treatment was accompanied by a decrease of SIL. A significant decrease was observed in organ localizations and in infections during remission of the leukaemia. SIL may be helpful as an auxiliary test in the management of leukaemic children.

Serum iron level (SIL) as well as that of other trace metals in neoplastic proliferations of the lymphoreticular system and leukaemias in children and adults has been the subject of numerous papers [2—5, 8—11, 13, 18—21]. An increase of SIL during the active period of acute leukaemia results from diminished utilization of iron in erythropoiesis which becomes inhibited by leukaemic metaplasis of bone marrow [4, 11, 13, 20]. Moreover, increase of SIL in acute leukaemia is caused by red cell haemolysis [3, 11, 20] and by release of the iron bound to the ferritin of destroyed leukaemic cells [3, 21]. Drugs applied in therapy can also inhibit the uptake of iron for haemoglobin synthesis [4, 14, 15]. The object of the present study was to investigate the SIL in the course of acute lymphoblastic leukaemia (ALL), to establish whether SIL could be used as an index of the activity of the disease, the efficacy of treatment, and of prognosis.

MATERIAL AND METHODS

SIL was studied in 57 children (31 boys and 26 girls) ranging in age from 2 to 15 years, treated for ALL [1, 15] from June 1, 1973, to October 15, 1974. In 24 untreated children with ALL, the SIL was determined on admission together with the haemoglobin level, red cell and thrombocyte count, quantitative and qualitative leukocyte count, bone marrow count and liver tests. The total number of SIL examinations was 267 (from 3 to 12 per case during the whole observation). SIL was not analysed in those children who 9 weeks before the examination had had a blood transfusion.

As a control group, 59 healthy age-matched children were studied (Table I). Venous blood samples were prepared and stored according to the norms required for iron determination [17].

SIL in serum deproteinized with 20% trichloroacetic acid was estimated by

TABLE I

Serum iron levels (in μg/dl) in controls, in marrow involvement and in complete remission in age groups A, B and C

Age group		A (2—5 yrs)			B (6—9 yrs)			C (10—15 yrs)		
		Normal	Marrow involvement	Remission	Normal	Marrow involvement	Remission	Normal	Marrow involvement	Remission
Number of observations		18	24	29	20	44	71	21	30	48
(Number of children)		(18)	(14)	(16)	(20)	(14)	(21)	(21)	(10)	(16)
Fe	$\bar{x}$	85.8	146.7	90.2	90.3	136.6	88.4	82.3	123.0	85.0
	(SD)	(13.2)	(63.6)	(28.9)	(16.3)	(42.5)	(23.0)	(14.8)	(37.6)	(19.8)

normal = SIL in healthy children
marrow involvement = SIL in children with ALL and more than 5% paralimphoblasts in the bone marrow
$\bar{x}$ = mean value
SD = standard deviation

means of atomic absorption spectrophotometry (Hilger-Watts Model H 1170) [7, 17]. The results were expressed in μg/dl iron as read from standard curves prepared by the use of metallic iron, trichloroacetic acid and deionized water [7, 17].

Mean SIL values were analysed according to age (Table I), the clinical stage of the disease (Table II) and to the degree of ALL activity (Table III). For statistical analysis, Student's *t* or the Welch test were applied after analysis of variance according to the F-Snedecor test [16].

RESULTS

I. SIL in controls, in bone marrow involvement and remission in age groups A, B, C (Table I)

Mean SIL values showed no significant differences between the particular age groups A and B, and C, c and A in healthy children, in bone marrow involvement and in remission, as well as between the control groups and the values obtained in remission of ALL. Values of SIL in all these age groups displayed an increase which was highly significant statistically ($p < 0.001$) in marrow involvement in comparison to the levels obtained in remission and in the controls.

II. SIL in the leukaemic stages (St) I to VIII (Table II)

The highest mean SIL value was obtained at the beginning of the first marrow involvement of ALL (169.3 μg/dl in St I). The mean SIL at the onset of the successive marrow relapses (131.8 μg/dl in St III) was significantly lower ($p < 0.01$) than in stage I. During treatment (St II, IV) leading to remission (St Va, Vb, V, VIII) SIL reached normal values. During treat-

TABLE II

Serum iron levels (μg/dl) in clinical stages of acute lymphoblastic leukaemia

No. of stage	Clinical stage of ALL	Number of observations (of children)	SIL $\bar{x}$ (SD)	Per cent marrow parablasts
I	1st marrow involvement (before treatment)	24 (24)	169.3 (52.8)	89.4
II	1st marrow involvement during intensive treatment	18 (14)	108.0 (41.4)	38.6
III	Onset of marrow relapses (2nd to 7th) during remissive treatment	34 (18)	131.8 (47.1)	70.7
IV	Marrow relapses (2nd to 6th) during intensive treatment	23 (13)	121.4 (37.1)	34.4
Va	1st complete remission	74 (34)	89.7 (25.2)	2.5
Vb	Remissions: 2nd to 6th	21 (11)	83.7 (23.1)	3.2
V	Remissions (jointly) from 1st to 6th	95 (41)	88.4 (25.4)	2.8
VI	Extramedullary relapse of ALL in marrow remission (CNS leukaemia, tumour of testes, kidneys)	25 (14)	71.6 (29.0)	3.6
VII	Bacterial or viral infections during remission	24 (16)	70.8 (21.7)	2.3
VIII	1st long lasting marrow remission over 3 years (6 observations after cessation of treatment)	26 (8)	93.1 (15.0)	2.5

ment, the values decreased, but differed significantly ($p < 0.001$) when compared in the following order: I and II, I and Va, IV and Vb, III and Vb. Mean SIL in stage I (169.3 μg/dl) was almost twice as high as that obtained during the first remission (St Va), 89.7 μg/dl. The decrease of SIL in the extramedullary relapse of ALL (St VI) amounted to 71.6 μg/dl and in the course of infections during remission (St VII) to 70.8 μg/dl; the difference was significant statistically ($p < 0.005$) in comparison to the 88.4 μg/dl mean value during the 1st to 6th remission in St V. SIL in St Va (1st remission) when compared with that in St Vb (2nd to 6th remissions) as well as that in St Va with St VIII did not differ significantly ($p > 0.5$).

III. SIL and marrow parablast percentage in relation to ALL activity (Table III)

The increase of SIL with progression of the disease appeared to be significant statistically and went almost parallel to the increase in the marrow parablast count. In the more

TABLE III

Serum iron values and marrow parablast percentage in relation to the degree of disease activity

Group range of marrow parablasts — per cent		I (0—5)	II (6—25)	III (26—100)	IV (26—100)
Number of observations (of children)		31 (23)	23 (17)	54 (27)	20 (15)
Fe μg/dl	$\bar{x}$	83.1	100.3	122.4	164.0
	(SD)	(20.9)	(33.2)	(20.6)	(47.0)
Parablasts per cent	$\bar{x}$	3.1	14.3	73.4	90.25
	(SD)	(1.52)	(5.4)	(18.7)	(9.55)

I. Complete remission. Results of SIL excluded in VIth and VIIth stage of ALL (Table II)
II. Imminent relapse or improvement during treatment
III. 1st bone marrow involvement or relapse
IV. Marrow involvement with peripheral hyperparablastosis from 21 to 231 thousand/mm^3 and/or leukaemic infiltration of testes, kidneys, mediastinal tumours and hepatosplenomegaly

advanced stages the differences in SIL were greater and more significant statistically ($p < 0.001$). The highest mean value, 164.0 μg/dl, was observed in marrow involvement with peripheral hyperblastosis and extramedullary localization of ALL (group IV).

DISCUSSION

The significant prolongation of survival of children with ALL has made it necessary to work out tests of the disease activity and efficacy of treatment.

For that reason the following tests have been recommended: 5-amino-4-imidazole carboxamide level in urine, fetal haemoglobin in blood, cytochemical PAS reaction, ferritin, transferrin and coeruloplasmin levels in serum as well as serum iron, copper, zinc, magnesium and silver [3, 4, 5, 8, 9, 11, 18—21] estimations. The data on SIL in ALL mostly deal with the period before treatment [3, 11, 13] and some with the period following remission [20].

The values shown in Table I indicate that mean SIL values are influenced by the disease itself and not by the age of the patient.

The classification into clinical stages from I to VIII is an attempt at systematizing the clinical course of ALL (Table II). The highest SIL was seen in St I, i.e. before therapy. The mean value obtained in that stage (169.3 μg/dl) was the highest beside that noted in the stage of marrow relapse with peripheral hyperparablastosis and/or leukaemic tumours (Table III). The decrease of SIL to normal during treatment is connected with the clinical and haematological improvement and with the gradual fall of marrow parablasts to below 5% (Table II).

SIL in bacterial or viral infections during remission (St VII) was similar as in other neoplastic conditions [3, 4, 11, 13]. The decrease of SIL in cases of an isolated organ localization of ALL (St VI) was like that observed in Hodgkin's disease and in other solid tumours [4, 10, 11, 13].

In the present work, it has been attempted to determine whether the SIL was influenced during the course of ALL. As it is seen in Table III, the mean SIL values increased parallel with the increase in the marrow parablast count. This must have been due to the inhibition of erythropoesis by the leukaemic marrow metaplasia [4, 11, 13, 20]. One of the highest mean SIL values (164.0 μg/dl) was observed in marrow involvement accompanied by peripheral hyperparablastosis and/or leukaemic infiltration of the organs (Table III), i.e. prognostically unfavourable signs [1, 6]. The cause of this is probably the fact that iron originates from the ferritin of parablasts circulating in the blood after their destruction [3, 21]. The highest SIL in group IV may have resulted from neoplastic infiltration of the liver which may additionally disturb iron metabolism.

The presented results do not fully explain the disorders of iron metabolism in ALL. They allow, however, some practical conclusions. Thus,

(i) increased SIL in ALL shows a positive correlation with the activity of the disease;

(ii) effective therapy and haematological improvement cause a decrease of SIL to normal values;

(iii) a high SIL value early in ALL may point to an unfavourable prognosis;

(iv) SIL may give some information of the degree of marrow involvement by the leukaemic process as well as of organ localizations and infections during remission.

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L. Legutko, M. D.
Krowoderskich Zuchów 23/103 St.
31—271 Kraków, Poland