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Zinc Deficiency in Hodgkin's Disease

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Abstract—*Serum, plasma, RBC and hair zinc concentrations were measured in children with Hodgkin's disease at diagnosis and during remission. Zinc values in all the measured compartments were found to be significantly low before treatment while serum, and plasma zinc levels returned to normal or above normal values during remission. Our results indicate that chronic zinc deficiency exists at diagnosis in Pediatric Hodgkin's disease in Turkey. In view of the recent observations indicating a close relationship between thymus and zinc, following hypothesis was speculated; a pre-existing nutritional zinc deficiency commonly found in Turkey may prepare a milieu favouring development of Hodgkin's disease by causing the suppression of thymus dependant cellular immunity.*

INTRODUCTION

INCREASED serum copper (Cu) levels in malignant lymphoma has been studied extensively. However, the literature on zinc metabolism in Hodgkin's lymphoma is controversial and very few in pediatric age group [1–7].

Our preliminary studies have indicated that serum zinc levels were consistently low in all clinical stages and types of Hodgkin's disease (HD), in Turkish children [7].

Recent animal and human studies have shown that the cellular immune response is depressed by zinc deficiency [8, 9, 10, 11].

Therefore serum plasma, erythrocyte and hair zinc concentrations in children with Hodgkin's disease were measured in order to evaluate the distribution of this trace element in different body compartments.

MATERIALS AND METHODS

Sixteen patients, under 15 yr of age with biopsy proven Hodgkin's disease, were included in this study. Zinc levels were determined at the time of diagnosis before any treatment. Nine patients had mixed cellularity, 3 nodular sclerosis, 2 lymphocyte predominence type of disease and one case was unclassified. Rye classification was used in staging [12]. Of 16 patients, 6 were stage IV, 6 were stage III, 1 was stage II and 2 were in stage I. One case could not be staged due to early discharge from hospital.

The serum, plasma, erythrocytes and hair zinc concentration were measured by using Atomic Absorption Spectrophotometer (Perkin–Elmer Model 103). The serum and hair zinc determinations were performed according to the methods previously described [7, 13]. The plasma and erythrocyte zinc concentrations were measured by modifying the method described by Rosner and Gorfien [6]. All readings were carried out in triplicate and the mean value was obtained for each sample. The results were highly reproducible. Serum copper levels were simultaneously measured. Serum zinc determinations were repeated before and during therapy and after complete remission, while plasma RBC and hair zinc assays were performed before treatment and during remission. Twenty, age and sex matched healthy children were used as controls.

RESULTS

The mean serum zinc concentration in 20 control and 15 untreated Hodgkin's patients is illustrated in Fig. 1. The mean serum zinc level in 15 patients was (87.26 ± 4.8 $\mu g\%$), significantly lower than the controls (110.5 ± 3.3 $\mu g\%$) ($P < 0.001$).

The mean plasma zinc level in 16 newly diagnosed cases was 89 ± 4.6 $\mu g\%$ and this was also significantly lower than the control values: 114.0 $\mu g \pm 3.36\%$. ($P < 0.001$) (Table 1).

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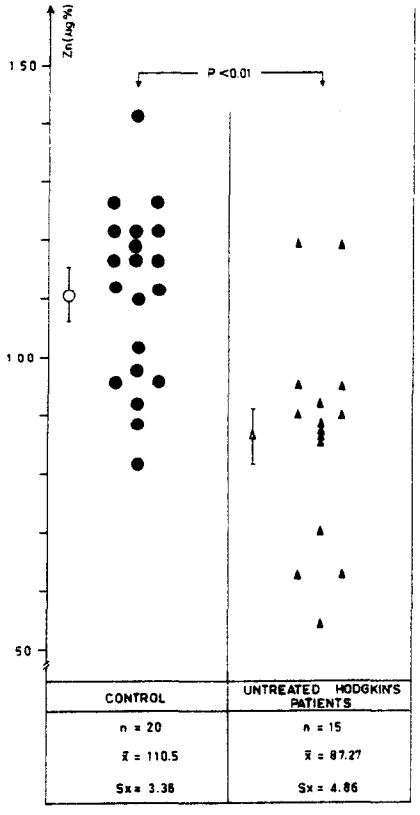

Fig. 1. Serum zinc levels.

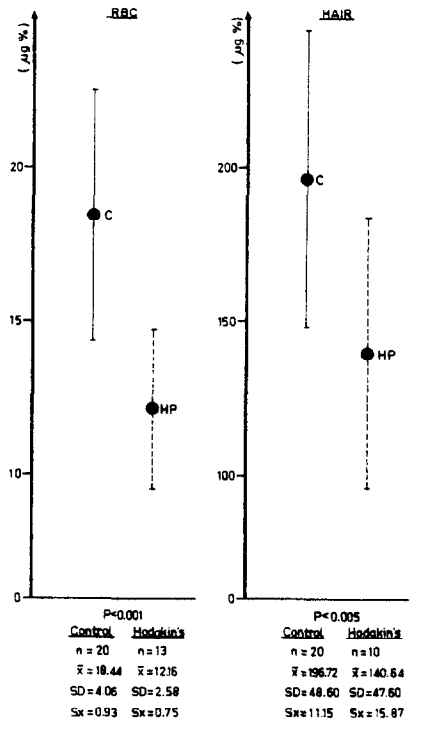

Fig. 2. Zn values in Hodgkin's patients.

Table 1. Plasma Zn levels in Hodgkin's disease

	Control ($\mu g\%$)	At diagnosis ($\mu g\%$)
n	20.00	16.00
$\bar{x}$	114.00	89.00
$S\bar{x}$	3.36	4.60
P	← <0.001 →	

The erythrocyte (RBC) and hair zinc levels, measured on 13 and 10 Hodgkin's patients respectively are presented in Fig. 2. The mean erythrocyte zinc was 12.16 ± 2 µg/ml of RBC and it was significantly lower than the control values of 18.44 ± 4.06 µg/ml of RBC ($P < 0.001$). The mean hair zinc level was 140.64 ± 47.6 µg/g of hair in HP, whereas the mean normal value was 196.72 ± 48.6 µg/g of hair. The difference between two mean values was also statistically significant ($P < 0.005$).

The plasma zinc levels of 14 patients with Hodgkin's disease who achieved complete remission is shown in Fig. 3. Plasma zinc levels returned the normal values during remission with a mean level of 113.0 ± 37 $\mu g\%$. However,

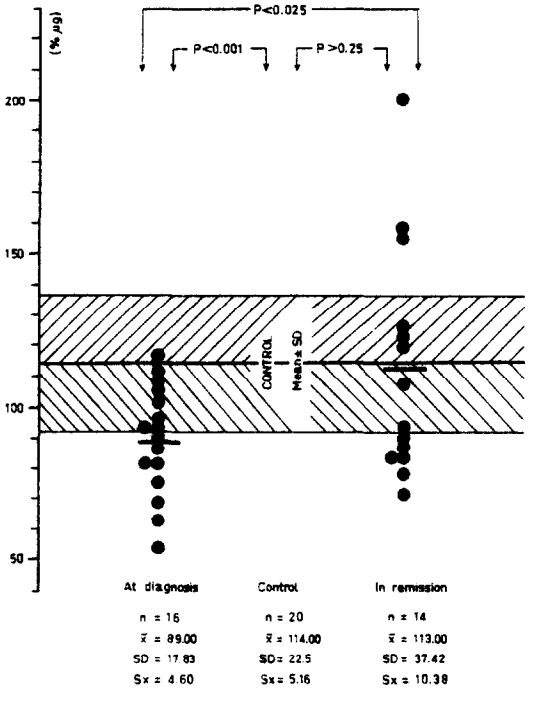

Fig. 3. Plasma Zn values in Hodgkin's disease.

the erythrocytes and hair zinc levels remained low during remission with the mean values of 12.97 ± 1.95 µg/ml and 135.08 ± 31.5 µg/g respectively (Table 2).

Table 2. Zinc levels in RBC and hair from children with Hodgkin's disease and normal controls

	Control				Hodgkin's at diagnosis				Hodgkin's at remission			
	n	$\bar{x}$	±	Sx	*n*	$\bar{x}$	±	Sx	*n*	$\bar{x}$	±	Sx
RBC	20	18.44	±	0.75	13	12.16	±	0.75	10	12.97	±	0.65
				$P<0.001$				$P>0.1$				
				$P<0.001$								
Hair	20	196.72	±	11.15	10	140.64	±	47.6	10	135.08	±	10.50
				$P<0.005$				$P>0.1$				
				$P<0.005$								

DISCUSSION

Changes in serum copper levels in Hodgkin's disease has been studied by a number of investigators [1, 2, 3, 14]. However, plasma, hair and erythrocyte zinc levels have not been studied in children with this disease.

The zinc values in serum, plasma erythrocytes and hair of Hodgkin's patients, in this study, were significantly lower than the normal children.

The data on serum and RBC zinc concentrations measured in adult patients with lymphoma has been controversial [4, 5, 6, 15].

Recently, Bucher and Jones reported the copper–zinc ratio (CZR) in patients with malignant lymphoma. The mean value of CZR was slightly high for patients with Hodgkin's disease and correlated well with disease activity [15].

The biological basis for the abnormalities in blood and hair zinc concentration, disclosed by the present study is unknown. However, it is generally accepted that a decrease in zinc concentration of plasma, erythrocytes, urine and hair is diagnostic for long standing zinc deficiency in man [16].

Chronic zinc deficiency is not well understood in Hodgkin's disease. However, the depressing effect of copper on zinc [17] and an antagonism between zinc and copper at the absorptive level has also been indicated [15, 16]. Therefore increased serum copper in untreated Hodgkin's disease, might be the cause of zinc deficiency in this disease. Serum copper levels return to normal when patients achieve remission in Hodgkin's disease [2, 3, 14]. Present study also disclosed increased serum zinc and decreased Cu levels in remission (Fig. 3). Low zinc values were observed in blood and hair prior to any therapy. Therefore decreased zinc concentration in these compartments could not be attributed to therapy but it may be part of the disease process. Elevated levels of serum and plasma

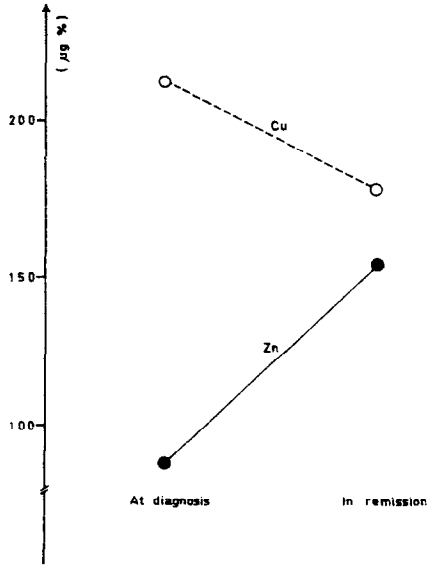

Fig. 4. Copper and zinc levels in Hodgkin's patients.

zinc, during remission supports this hypothesis. The increase in zinc plasma level in remission is unclear. It may be the result of dissociation in the zinc–protein complex secondary to tissue breakdown during therapy.

Another possibility could be an accumulation of zinc in tumor tissue. Rosoff and Spencer [18, 19] studied the affinity of Zn^{65} to the tumor and the normal tissues in cancer patients. Tumor tissue, located in organs other than the liver, had somewhat greater uptake of Zn^{65} than the corresponding normal tissues. They claim the zinc concentration may depend on the cytological type of the tumor [19]. The deficiency of zinc may lead to alterations in cellular function and structure and ultimately result in neoplasia in the tissue where this trace metal has a special metabolic function [19].

Zinc is an important trace mineral for the development of thymus and the recent observations by Fraker *et al.* shows dietary zinc deficiency causes severe atrophy of the thymus in rats and pigs [20]. Andresen and his colleagues also drew attention to a syndrome in calves which is characterized by symptoms associated with zinc deficiency and severe hypoplasia of the lymphoid system [8]. The immune system of these animals, could be restored by treatment with zinc oxide. Hsu and Antony have recently shown, that zinc deficiency has variable effects on the DNA synthesis at different tissues [21]. The thymus gland was reduced in size more than any other organ in zinc deficient animals [10].

In one study carcinogenesis could be inhibited by dietary zinc supplement [2]. Malnourished infants and the children with acrodermatitis enteropathica (AE), have thymic atrophy. The impaired cell mediated immunity associated with zinc deficiency in these entities respond dramatically to zinc therapy [10, 11, 23].

Zinc also is known to act as a nonspecific mitogen in lymphocyte cultures. The blastogenic transformation of lymphocytes increased by zinc added to the culture media and this effect was comparable to PHA. Zinc is the only mitogen that is naturally present in human body. A major regulating role of zinc in lymphocyte proliferation during pre- and post-natal life has been suggested [9, 10].

DNA and RNA polymerases, reverse transcriptase and "thymidine kinase" are zinc containing enzymes. It appears, enhanced DNA synthesis and mitoses of lymphocytes by zinc, is related to an increased activity of these enzymes [13, 24, 25].

Cellular immune deficiency in Hodgkin's disease is not well understood. Immune deficiency in healthy twin siblings of patients with Hodgkin's disease and the familial Hodgkin's cases suggest the immune deficiency in this lymphoma is partly caused by genetic and/or environmental factors and an immune deficiency may be present prior to the development of the Hodgkin's lymphoma, further aggravated by the disease process [26, 27].

In humans, lymphoma clearly predominates in both primary and secondary (drug induced) immune deficiency states [28].

Nutritional zinc deficiency is common in Turkish children [29, 30] and the relative frequency of Hodgkin's disease is also high in the same population [12]. There could be a possible cause–effect relationship between these two entities which needs further clarification.

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