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Serum Lactate Dehydrogenase (LDH) Activity in Children with Malignant Diseases

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Objective: The measurement of the level of LDH activity in the serum was performed on children with different types of malignant disease and relation between LDH levels and response to chemotherapy was investigated.

Method: Serum lactic dehydroygnase (LDH) levels were measured at diagnosis in 53 patients with different types of malignant diseases and in 37 healthy children matched for age and sex as controls.

Result: The mean LDH level was significantly higher in acute lymphoblastic leukemia (ALL) (P<0.001) as compared to other groups of malignancy. Higher LDH levels in ALL were associated with high leukocyte counts and blast cells (r=0.46, P<0.04, and r=0.84, P<0.001) respectively. A significantly reduced level of LDH was observed in ALL only after induction of chemotherapy (P<0.01). In solid tumors however, specially lymphoma (NHL, Hodgkin's), high LDH levels correlated with extent of tumor mass or stage of disease.

Conclusion: Early measurement of serum LDH could be useful in identifying response to chemotherapy so it is important to determine the prognostic value of this biological marker.

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Lactic dehydrogenase (LDH), a pyridine-linked enzyme found in virtually all animal and human tissues, functions primarily in the metabolism of glucose, catalyzing the reduction of free pyruvate to lactate during the last step of glycolysis, as well as the conversion of lactate to pyruvate during gluconeogenesis. Its concentration is highest in liver followed in descending order in skeletal muscle, heart and kidney[1]. Malignant cells have a distinctive type of

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metabolism in which the glycolytic sequence and the tricarboxylic acid cycle are poorly integrated, hence the cells tends to utilize from five to ten times as much glucose as do normal tissues, converting most of it into lactate[2]. Whether the increased serum levels of LDH commonly found in cancer patients reflect greater production and release of the enzyme by malignant cells[2], is not clear. Lactic dehydrogenase (LDH) exists in many different cell systems and subsequent to tissue or cell damage, serum LDH levels may be elevated. A relationship between neoplasia and increased LDH levels has been reported by many worker's in both human and animal tumors[3,4]. Elevated LDH levels are encountered in neoplastic tissue as well as in the serum of patients with a variety of epithelial tumors. High levels of serum LDH have been observed in patients with solid tumors, leukemia, diffuse symptomatic lymphoma, (in non-Hodgkin's Lymphoma, particularly Burkett's lymphoma)[5,6], small cell lung cancer[7] and testicular neoplasm. LDH appears to have a good correlation with disease activity and tumor mass[8-10]. In osteosarcoma the serum lactate dehydrogenase may be elevated in about 30% of patients even without metastases and may be a useful marker for response to treatment but in Ewing's sarcoma an elevated LDH at diagnosis appears to correlate with poor outlook[11].

In this study the measurement of the level of LDH activity in the serum was performed on children with different types of malignant disease and relation between LDH levels and response to chemotherapy was investigated.

METHODS

This study was conducted from May 2000 till February 2001 on a total of 53 patients with recently diagnosed malignancies who were admitted to Maternal and Child Hospital. The included cases were; acute leukemia 28 (24 lymphoblastic (ALL) and 4 myloblastic (AML)), two cases were chronic mylocytic leukemia (CML), lymphoma 12 (6 Non-Hodgkin's lymphoma (NHL) and 6 Hodgkin's lymphoma (HL)), Rabdomyosarcoma 4, Neuroblastoma 2, Ewing sarcoma 2, brain tumor 1, Retinoblastoma 1, and Teratoma 1. Their ages ranged from 1 to 15 years. Thirty seven, apparently healthy children matched for age and gender served as controls.

All patients had a comprehensive diagnostic work up for typing of leukemia and staging for other malignances. Those patients were receiving chemotherapeutic treatment in a uniform manner according to their types of malignancy. Serum LDH levels were determined at the time of the diagnosis and after four weeks of starting chemotherapy by using kits from Randox, U.K.

Results are expressed as mean $\pm$ SD. Differences between malignant and control groups were assessed using the Student's t test. Differences between variables in the different groups were assessed using one-way analysis of variance (ANOVA). Regression and correlation analyses between variables were performed by calculating Pearson's correlation coefficients (r). Differences in the number of subjects with and without malignancy were investigated using chi square (X^2) with Yates's correction. P values of > 0.05 were considered not significant.

RESULTS

Age and sex distribution of all malignant cases and control groups are summarized in Table 1. Statistically, there was no significant difference between both groups. The serum LDH levels in all cases of malignant diseases and the control group are presented in Table 2. The mean serum level of LDH was: acute lymphoblastic leukemia , ALL (562 ± 161 IU/L), AML (375 ± 96 IU/L), CML (418 ± 11 IU/L), lymphoma; NHL (363 ± 96 IU/L), Hodgkin lymphoma (283 ± 53 IU/L), Rhahdomysarcoma (343 ± 47 IU/L), neuroblastoma (330 ± 93 IU/L), Ewing's sarcoma (178 ± 60 IU/L) while in the control group it was (192 ± 58 IU/L). Data in most malignant cases demonstrated an extremely significant increase in serum LDH activity as compared to the non – malignant or the control group ($p < 0.0001$). Within the malignant groups, the highest LDH activity was observed in ALL cases, while the lowest was in Ewing's sarcoma. The elevated LDH level in ALL cases was found highly significant as compared to Hodgkin's lymphoma and Ewing's sarcoma ($p<0.001$). Whereas, it was only significant compared to NHL and Rhahdomysarcoma ($p<0.01$), and neuroblastoma ($p <0.05$). However, it was insignificant compared to the remainder of malignant cases.

Table 1. **Age and sex distribution of case and control groups**

Age (Year)	Control (37)		Patients (53)	
	Male	Female	Male	Female
<1	1	--	1	1
1-5	6	6	15	8
>5	11	13	15	13
Total	18	19	31	22

Table 2. **Mean level of serum LDH in different types of malignancy and control**

Type of Malignancy	No. of Patients	Serum LDH Activity (IU/L)	
		Range	Mean ± SD
ALL	24	320-780	562 ± 161
AML	4	325-460	375 ± 96
CML	2	410-425	418 ± 11
Lymphoma	6	200-475	363 ± 94**
Hodgkin's	6	220-325	288 ± 53***
Rhabdomyosarcoma	4	280-390	343 ± 47*
Neuroblastoma	2	260-400	330 ± 99
Ewing's sarcoma	2	135-220	178 ± 60**
Brain tumor	1	250	250
Retinoblastoma	1	310	310
Teratoma	1	390	390
Controls	37	110-350	192 ± 56***

ALL cases versus other malignant cases and controls
**P<0.05, **P<0.01, ***P<0.001*

Pearson correlation analysis of serum LDH among children with acute lymphoblastic leukemia (ALL), showed a highly significant correlation between LDH levels and white blood cell counts ($r = 0.46$, $p < 0.04$) and the number of blast cells ($r = 0.8$, $p < 0.001$) as compared to similar analysis among children with AML or CML (Table 3). However, there was no relationship between LDH levels and WBC or blast cells in any of the other malignant groups.

Table 3. **Correlation of LDH activity with WBC and blast cell in children with different types of leukemia**

Types of leukemia	WBC count		Blast cell	
	R	P	R	P
ALL	0.46	<0.04	0.8	<0.001
AML	0.6	NS	0.6	NS
CML	0.5	NS	0.3	NS

Table 4 showed the activity or stage of solid tumors in relation to mean serum LDH level. High LDH level was observed in stage III, IV specially in non-Hodgkin lymphoma, but there were no differences regarding other types of solid tumors and statistical analysis was not performed due to small sample size.

Table 4. **The activity or stage of solid tumors in relation to mean serum LDH (IU/L) level**

Type No.	Stage	LDH activity before remission	LDH activity after remission
Lymphoma NHL (6)	II	220	--
	III	300	--
	III	350	320
	IV	390	360
	IV	445	240
	IV	475	325
Hodgkin's (6)	II	220	--
	II	325	170
	II	325	300
	II	330	--
	III	220	--
	III	310	275
Rhabdomyosarcoma (4)	II	340	--
	IV	380	--
	IV	360	--
	IV	390	360
Retinoblastoma(2)	II	310	300
	IV	390	--

The effect of chemotherapeutic treatment is presented in Table 5, which showed the mean serum levels of LDH in different types of malignancies before and after induction of chemotherapy or remission. The response to treatment was observed by the decrease in LDH activity. This decrease was statistically highly significant in ALL ($P < 0.01$) but not significant regarding other types of malignancy.

Table 5. **Mean level serum LDH before treatment and after remission in different types of malignant cases**

Type of Malignancy	No.	LDH activity (IU/L)		P value
		Before	Remission	
ALL	13	520 ± 165	303 ± 90	0.01 (S)
AML	1	460	350	
CML	1	425	265	
Lymphoma	3	405 ± 64	331 ± 25	NS
Ewing's sarcoma	1	135	125	
Neuroblastoma	1	260	290	
Rhabdomyosarcoma	1	390	360	
Hodgkin's	3	320 ± 69	248 ± 69	NS
Retinoblastoma	1	310	300	

Results are mean ± SD

DISCUSSION

A marked increase in serum LDH level has been observed in the past in neoplastic diseases by several authors, although no clear correlation has been established either with a specific disease or any clinical parameter[12]. In this prospective study, serum LDH levels were determined in children with different types of malignancy, their ages range from less than one year up to fifteen years, and, in thirty-seven healthy children matched for age and sex who served as controls.

Mean LDH levels were markedly elevated in patients with leukemia especially acute lymphoblastic leukemia (562 ± 161 IU/L) followed by chronic mylocytic leukemia (418 ± 11 IU/L) and finally acute myeloblastic leukemia (375 ± 96 IU/L). It was statistically highly significant ($P<0.001$) in acute lymphoblastic leukemia only when compared to those obtained for other groups or the controls. Our results were similar to those obtained from Kornbery and Polliak[3], and Sactor, et al[13]. The result could be explained as LDH levels will frequently be elevated due to leukemic cell lysis, although hepatomegaly may be accompanied by mild abnormalities of liver function tests[14], or increased cellular LDH activity reflects a glycolysis in the cytoplasm of malignant cell accompanied by high turnover rate[15].

In the present study, high LDH levels in acute lymphoblastic leukemia (ALL) correlated with leukocyte counts and blast cells that were statistically significant ($P<0.04$, and 0.001 respectively). However, no agreement was found by Ching-Honpui[1] as their study showed that serum LDH levels in children with acute lymphoblastic leukemia were roughly correlated with leukocyte counts but not with the percentage of blast cells. These observations were explained in that the

total body burden of leukemia cells is a more important determinant of serum LDH level than the cell proliferative rate[16].

In patients with other types of malignant diseases especially lymphoma (NHL & Hodgkin's), correlation with activity or stage of disease was found, even though, statistical analysis couldn't be done due to small sample size. Similar results were observed by Aresneau et al[17], who found that the LDH level in lymphoma correlated with tumor mass. In addition, another study[18] reported that serum LDH levels, which may reflect the mass of tumor present, were lowest in patients with localized disease. This could explain the markedly elevated levels of serum LDH in untreated patients with large tumors.

With regards to the recognition of LDH level before and after induction of chemotherapy, it was found that in acute lymphoblastic leukemia there was a significant reduction in mean LDH level (303 ± 90 IU/L), 4-6 weeks after induction of chemotherapy ($P < 0.01$). This reduction was not significant regarding other types of malignancy. Simore et al[19] and Miller et al[20] reported in their study that LDH in acute lymphoblastic leukemia serve as the best predictors of treatment outcome.

CONCLUSION

In conclusion, evaluation of LDH level in patients with acute lymploblastic leukemia could represent an additional and useful parameter in determining the clinical and prognostic aspect of the disease.

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