Original Research Article

Electrophoretic pattern of LDH isoenzymes in different hematological malignancies at a cancer unit

Sneha Henry[1*], Bewin Oral J[2], Goldy S J[3]

[1]Assistant professor, Department of Biochemistry, Sree narayana institute of medical sciences, Ernakulam, Kerala 683594, INDIA.
[2,3]Associate professor, Department of Microbiology, {Department of Obstetrics and Gynecology}, Sree Uthradom Thirunal Academy of Medical Sciences, Vattappara, Thiruvananthapuram, Kerala 695028, INDIA.
Email: Snehahnry@yahoo.co.in , bewin.grace@gmail.com , goldybewin@gmail.com

Abstract

Background: Lactate Dehydrogenase (LDH) is the key enzyme in Lactic Acid production and degradation which is an end product of anaerobic glycolysis. LDH is one of the enzyme systems preferentially produce and is retained by cancer cells as it is necessary to maintain tumor growth. When LDH isoenzymes are released from neoplastic tissue in serum, the LDH isoenzyme patterns are affected by its levels in serum. The present study is to assess the isoenzyme patterns of LDH, in various malignancies and stages at presentation, to see the preponderance of the type of isoenzymes. **Material and Methods:** The present study was a prospective, observational study, conducted in the Department of Biochemistry and the Department of Clinical Hematology and Bone Marrow Transplant Unit, Christian Medical College and Hospital, Ludhiana, in diagnosed patients of Hematological Malignancies who were on treatment. LDH isoenzymes were separated and quantified by agarose gel electrophoresis using the method described by Barnett H method with barbiturate buffer at pH 8.6 .Statistical analysis was done using descriptive statistics. **Results:** 100 hematological malignancy patient samples received in the Biochemistry laboratory were collected and their isoenzyme patterns were studied by electrophoresis. 67% were males and the rest 33% patients were females. Maximum numbers of patients were between the age group 41-70 years which accounted for 58% of the subjects. AML and MM had maximum number of patients of 36 and 31 respectively. ALL and CLL had the least number of patients that is 6 and 7 respectively. 56 patients had LDH values less than 480U/L and 44 patients had LDH values more than 480U/L. Isoenzyme 1 shows maximal distribution of 58%. 90 % of the patients had an increase in isoenzyme pattern and 5% had decrease in pattern. LDH isoenzyme 1 has maximum value among all the malignancies. Isoenzyme 4-5 had lesser representation. LDH 1 is the most prominent isoenzyme in NHL and non NHL DLBCL and in other lymphomas, and HL had increase LDH 3. LDH 2 had maximum decrease in NHL and non NHL DLBCL. **Conclusion:** All hematological malignancies had increase in LDH 1 with the exception of AML patients who had increase in LDH 4. The increase in LDH 1 was seen in ALL, CML, CLL, lymphomas and multiple myeloma, while LDH 2 was decreased in ALL, AML, lymphoma and MM. LDH 1 isoenzyme is most prominent to be raised in malignancies.
Key Words: Lactate Dehydrogenase, LDH isoenzyme, AML, Multiple myeloma, hematological malignancies,

[*]**Address for Correspondence:**
Dr Sneha Henry, Assistant Professor, Department of Biochemistry, Sree narayana institute of medical sciences, Ernakulam, Kerala 683594.
Email: Snehahnry@yahoo.co.in
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INTRODUCTION

Lactate Dehydrogenase (LDH) is a hydrogen transfer enzyme that catalyzes the oxidation of lactate to pyruvate with NAD+ acting as the hydrogen acceptor.[1,2] LDH is the key enzyme in Lactic Acid production and degradation which is an end product of anaerobic glycolysis. Leakage of the enzyme from the damaged tissue increases the levels of LDH in the serum, which is the basis of using it as a diagnostic marker to tissue damage.[2] Various cytokines have been reported to alter the LDH isoenzyme profile by enhancing synthesis of one of the monomers.[3] The LDH

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isoenzymes are numbered 1 – 5 depending on their electrophoretic mobility. LDH is one of the enzyme systems preferentially produce and is retained by cancer cells as it is necessary to maintain tumor growth. When LDH isoenzymes are released from neoplastic tissue in serum, the LDH isoenzyme patterns are affected by its levels in serum. There have been reports of anomalies in the synthesis and the total LDH activity of LDH isoenzymes patterns that correlate with cancers.[4] A Study done on Acute Myeloid Leukemia patients on chemotherapy to find factors of prognostic importance, it was found that the only variable of statistical importance was LDH levels ≥ 400 U/ml which was significantly related to mortality rate.[5] The utility of LDH isoenzymes in diagnosis of malignant and non malignant ascites showed that LDH 4 and LDH 5 levels were higher in malignant ascites when compared to non malignant ascites. LDH showed 96% sensitivity and 76% specificity for diagnosis of malignant ascites.[6] Serum LDH is an important prognostic factor in patients with Non-Hodgkin's lymphoma (NHL). High LDH levels is one among other factors like age, staging etc, which is included in the International Prognostic index of aggressive NHL which can predict the 5 year survival of patients.[7] The study of LDH isoenzymes is indicative of the diseased tissue depending on the electrophoretic pattern. The present study is to assess the isoenzyme patterns of LDH, in various malignancies and stages at presentation, to see the preponderance of the type of isoenzymes.

MATERIAL AND METHODS

The present study was a prospective, observational study, conducted in the Department of Biochemistry and the Department of Clinical Hematology and Bone Marrow Transplant Unit, Christian Medical College and Hospital, Ludhiana. Study period was from 31st December 2011 till 30th November 2012 (1 year). Institutional ethical committee approval was obtained for present study.

Inclusion criteria -

Diagnosed patients of Hematological Malignancies who were on treatment Presenting symptoms, duration of illness, clinical diagnosis and associated complications were retrieved from the medical record files of the respective patients. The blood samples for the serum LDH and its isoenzyme pattern were collected under complete aseptic condition from the antecubital vein. The samples were transported to the laboratory immediately and serum was separated after centrifugation of the sample. Samples were stored at 4°C after their total LDH levels is estimated. They were later processed by electrophoresis to detect the isoenzyme patterns by Barnett H method 9 with barbiturate buffer at pH 8.6. The serum LDH levels were estimated on Modular P-800 auto-analyzer, using kits supplied by ROCHE. The method was by UV-assay, based on the formulation described by the German Society for Clinical Chemistry, Deutsche Gesellschaft für klinische Chemie. (DGKC) in 1972.26LDH isoenzymes were separated and quantified by agarose gel electrophoresis using the method described by Barnett H method with barbiturate buffer at pH 8.6 .[8] The data obtained was subjected to statistical analysis using computer software (SPSS version 20; Chicago Inc., USA). The qualitative data were expressed in proportion and percentages and the quantitative data expressed as mean and standard deviations. Statistical analysis was done using descriptive statistics.

RESULTS

100 hematological malignancy patient samples received in the Biochemistry laboratory were collected and their isoenzyme patterns were studied by electrophoresis using the Barnett H method [8] with barbiturate buffer at pH 8.6. Out of the total 100 patients included in our study, 67 patients (67%) were males and the rest 33 patients (33%) were females.

Table 1: Distribution Of Patients According To Gender

Gender	Number of cases	Percentage (%)
Males	67	67
Female	33	33
Total	**100**	**100**

The subjects were in the age range of 6 to 90. Maximum numbers of patients were between the age group 41-70 years which accounted for 58% of the subjects while the least number of patients were in 81-90 years age group which accounted for only 1%.

Table 2: Distribution of Patients According To Age

AGE (IN YEARS)	NO.	PERCENTAGE
0-10	2	2
11-20	12	12
21-30	11	11
31-40	7	7
41-50	17	17

51-60	18	18
61-70	23	23
71-80	9	9
81-90	1	1
TOTAL	**100**	**100**

AML and MM had maximum number of patients of 36 and 31 respectively. ALL and CLL had the least number of patients that is 6 and 7 respectively.

Table 3: distribution of malignancies in patients

Malignancies	No. Of Patients
Chronic Leukemoid Leukemia	2
Chronic Myeloid Leukemia (CML)	6
Acute Leukemoid Leukemia (ALL)	8
Lymphomas	18
Multiple Myeloma (MM)	31
Acute Myeloid Leukemias (AML)	35
Total	**100**

The normal range for LDH is 240-480 U/L.[9] Hence we used 480 as the upper limit cutoff. 56 patients had LDH values less than 480U/L and 44 patients had LDH values more than 480U/L. Both patients of CLL had values less than 480U/L. 50% of patients with ALL had values less than 480U/L and the other half of patients had values more than 480U/L.

Table 4: Distribution of LDH enzyme values in different hematological malignancies

Malignancies	Percentage of patients with LDH value <480	Percentage of patients with LDH value >480
CLL (n=2)	100	0
MM (n= 31)	87	13
LY (n=18)	52.9	47.1
ALL (n=8)	50	50
AML (n=43)	38.2	61.8
CML (n=6)	16.6	83.4

Isoenzyme 1 shows maximal distribution of 58%. 90 % of the patients had an increase in isoenzyme pattern and 5% had decrease in pattern. The rest 5% of the patient's isoenzyme patterns lie in the normal range.

Table 5: Distribution of isoenzymes in study patients.

	ISOENZYME PATTERN		RANGE OF LDH ENZYME LEVELS IN THE
ISOENZYME	INCREASE	DECREASE	RESPECTIVE ISOENZYMES (U/L)
1 (n = 58)	55	1	102-5720
2 (n =15)	9	3	232-8599
3 (n =15	14	1	55-1638
4 (n = 6)	6	0	255-620
5 (n = 6)	6	0	314-679
TOTAL	**90**	**5**	**55-8599**

56 % patients had LDH value < 480 U/L, among them, in acute leukemia LDH 1 increased by 23.3% (10/43) and LDH 4 20.9% (9/43). In chronic leukemia LDH 1 increased by 37.5%. In lymphomas LDH 1and3 had increased by 27.7% and in MM LDH1 had increased by 51.6%. 44% of patients had LDH > 480 U/L, in acute leukemia LDH 1 had increased by 44.2 % (19/43) and LDH 4 by 34.9%. In chronic leukemia LDH 1 had increased by 50%. In lymphomas LDH 1 had increased by 27.7% and in MM LDH1 had increased by 9.6%. Overall LDH 1 isoenzyme levels were increased in both the groups.

Table 6: Increase levels of isoenzymes in the patients at different enzyme levels.

	LDH < 480 U/L (n=56)				LDH>480 (N=44)			
	AL (n=43)	CL (N=8)	LY (N=18)	MM (N=31)	AL (n=43)	CL (N=8)	LY (N=18)	MM (N=31)
ISO 1	10	3	5	16	19	4	5	3
ISO 2	2	0	0	3	0	1	4	1
ISO 3	4	1	5	8	6	1	3	0
ISO 4	9	1	1	9	15	2	4	0
ISO 5	4	2	3	5	4	0	2	0

56% patients had LDH value < 480 U/L, among them in acute leukemia LDH 2 had decreased by 34.9% and LDH 3 by 27.9%. None of the patients of chronic leukemia had decrease in LDH 1. In lymphomas LDH 2 (44.4%) had decreased and in MM LDH2 (74.1%) had decreased. 44% of patients had LDH > 480 U/L, among them in acute leukemia LDH 2 had decreased by 51.2%. In chronic leukemia LDH 1and2 had decreased by 50%. In lymphomas LDH 2and3 had decreased by 22.2% and in MM LDH3 had decreased by 12.9%. Overall in both groups LDH 2 levels decreased the most.

Table 7: Decrease Levels of Isoenzymes In The Patients At Different Enzyme levels.

	LDH < 480 U/L (n= 56)					LDH > 480 U/L (n=44)				
	AL (n=43)	CL (N=8)	LY (N=18)	MM (N=31)	TOTAL	AL (n=43)	CL (N=8)	LY (N=18)	MM (N=31)	TOTAL
ISO 1	1	0	2	3	9	4	0	2	1	11
ISO 2	15	2	8	23	48	22	4	4	3	33
ISO 3	12	2	4	15	33	6	2	4	4	16
ISO 4	3	1	4	7	15	5	0	1	2	8
ISO 5	1	2	2	4	9	6	0	0	0	6

The study has more individuals who are >21 years age group (86%). Patients of CLL, CML and MM were >21 years. Patients of ALL and AML had 50% and 26.5% young patients respectively.

Table 8: Distribution Of Malignancies Between Individuals <21 And >21 years.

AGE	ALL	AML	CLL	CML	LYMPHOMA	MM	TOTAL
< 21 YRS	4	9	0	0	1	0	14
≥21YRS	4	26	2	6	17	31	86
TOTAL	**8**	**35**	**2**	**6**	**18**	**31**	**100**

In AML patients who are less than 21 yrs isoenzyme 4 is the most prominent isoenzyme. In all the other patients isoenzyme 1 is the most prominent isoenzyme. In age group >21 years isoenzyme 1 is clearly the most prominent isoenzyme. LDH 1 is the most prominent isoenzyme in >21 yrs age group and also in most of the patients in age <21 yrs. LDH 2 had not increased in any patient in age group < 21 years. Out of the 35 AML patients 26 patients belong to > 21 yrs age group. 18 patients had increase in LDH 1 and 15 patients have increase LDH 4; indicating 7 patients in the same group have increased LDH1 and 4.

Table 9: Distribution of malignancies with their proportion of isoenzyme 1.

AGE	ALL		AML		CLL		CML		LYMPHOMA		MM		TOTAL
	T.No	Iso1	T.No	Iso1	T.No	Iso1	T.No	Iso1	T.No	Iso 1	T.No	Iso1	
< 21 YRS	4	3/4	9	4/9	0	0	0	0	1	1/1	0	0	14
≥21 YRS	4	3/4	26	18/26	2	2/2	6	6/6	17	9/17	31	19/31	86
TOTAL	**8**		**35**		**2**		**6**		**18**		**31**		**100**

LDH isoenzyme 1 has maximum value among all the malignancies. Isoenzyme 4-5 had lesser representation.

Table 10: Shows Frequency Distribution Of Isoenzymes In Different malignancies

ISOENZYMES	ACUTE LEUKEMIAS (n=43) %		CHRONIC LEUKEMIAs (n=8) %		LYMPHOMA (n=18) %		MULTIPLE MYELOMA (n=31) %		TOTAL
1	28	65.1%	5	62.1%	7	38.8%	18	58.1%	58
2	6	14.0%	1	12.5%	3	16.7%	5	16.1%	15
3	3	7.0%	2	25%	4	22.2%	6	19.3%	15
4	3	7.0%	0	0%	1	5.6%	2	6.5%	6
5	3	6.80%	0	0%	3	16.7%	0	o%	6
TOTAL	**43**	**100%**	**8**	**100%**	**18**	**100%**	**31**	**100%**	**100**

LDH 1 is the most prominent isoenzyme in NHL and non NHL DLBCL and in other lymphomas, and HL had increase LDH 3. LDH 2 had maximum decrease in NHL and non NHL DLBCL.

Table 11: Shows Isoenzyme Pattern In The Subgroups Of Lymphoma Patients.

LYMPHOMAS (n= 18)	NUMBER OF INCREASE IN ISOENZYME LEVEL					NUMBER OF DECREASE IN ISOENZYME LEVEL				
	ISO 1	ISO 2	ISO 3	ISO 4	ISO 5	ISO 1	ISO 2	ISO 3	ISO 4	ISO 5
NHL (n=5)	3	1	2	2	1	0	3	2	0	0
NON NHL DLBCL (n=5)	3	1	2	0	2	1	4	2	2	1
HL (n=4)	1	1	3	2	1	2	2	1	0	0
OTHERS (n=4)	3	0	1	0	1	1	3	2	3	1

DISCUSSION

Malignant cells have rapid multiplication of cells, hence the cells tends to utilize about five to ten times as much glucose as normal tissues do, therefore converting most of it into lactate. LDH levels correlated with number of blast during remission and relapse.[10] LDH is a strong pretreatment prognostic factor in these patients and it correlated with disease and survival status.[2] Bouafia F *et al.*.[7] studied 326 patients of different hematological malignancies, of which 252 were NHL, 28 HL, 17 CLL, and 16 myeloproliferative syndromes and 13 MM patients. The main biochemical parameters estimated were LDH enzyme levels and its isoenzymes by agarose gel electrophoresis. Males predominated in our study which was in accordance with Kornberg A *et al.*.[11] Dumontet C *et al.*.[12] had 172 patients of hematolocgical malignancies and the mean age was 59 years. Bouafia F *et al.*.[7] in their study on 326 patients reported age range of 15-89 years with a median age of 60 years. Similar findings were noted in present study. 56% of the patients had values in the normal range and 44% of the patients had values more than 480 U/L, this was similar to Bouafia F *et al.*.[7] whose study had 49% of patients with high serum LDH values. Kornberg A *et al.*.[11] studied the LDH values in different hematological malignancy patients and found that LDH in acute non lymphoblastic leukemia the range was 126-684 U/L, in acute lymphoblastic leukemia it was 402-3582 U/L, in patients with CML in blast crisis had levels of 970-1940 U/L. In present study 55 out of 100 patients (55%) had increase percentage of LDH isoenzyme 1. In acute leukemia 67.4% patients had increase in LDH 1. Of which ALL had 100% and AML 21/35 60% had increase in LDH 1. These findings corroborated with findings of Pandit MK *et al.*.[13] In chronic leukemia 87.5% patients had increase in LDH 1. Of which CLL 100% and CML 83.3% had increase in LDH 1. Similar findings were observed by Drexler HG *et al.*.[14] and Chirulescu Z *et al.*.[15] for CML and Bouafia F *et al.*.[7] for CLL patients. Whereas Muller cp *et al.*.[16] and Buchsbaum *et al.*.[17] observed an increase in LDH 5 and LDH 3 respectively in CML patients. In multiple myeloma 19/31 (61.3%) patients had increase in LDH 1, this is in agreement with Lin Na *et al.*.[3] In present study 15% had increase percentage of LDH 2. In acute leukemia 4.6% patients had increase LDH 2. In ALL 12.5% and in AML 2.9% had increase in LDH 2. Pandit MK *et al.*.[13] observed similar findings in ALL chemotherapy responders. In multiple myeloma 12.9% patients had increase in LDH 2. Lin Na *et al.*.[3] observed similar findings in MM patients with kidney disease. 15% patients had increase percentage of LDH 3. This is in corroboration with Bouafia F *et al.*.[7] study who had observed increase in LDH 3 in MM, CLL and NHL. In the present study one patient with Burkitt's lymphoma had increase in LDH 1, which was contrary to study by Csako *et al.*.[18] 6% had increase percentage of LDH 4. In acute leukemia 55.8% and in chronic leukemia 25% had increase in LDH 4. Which is in agreement with Patel *et al.*.[19] 6% had increase percentage of LDH 5. In our study are there was increase in LDH 5 in ALL, AML, lymphomas and CML with no increase CLL which is contrary to study by Rambotti P *et al.*.[20] LDH is a simple, prognostic test for malignancies. It is an enzyme synthesized by anaerobic glycolysis. Malignant cells have high levels of anaerobic glycolysis due to increase turnover of cells and is the main mechanism leading to increase levels of LDH. Levels increase as it is released from damaged tissue. The isoenzymes produced are organ specific hence increasing the diagnostic value. LDH 1-2 are increased in malignancies, the H shift could be due to increase production of lactic acid in these cells. Present study it was found high LDH values in the study group which comprised of patients of hematological malignancies with 55% of patients having high LDH 1 levels. Sampling in our study was done irrespective of the stage of the illness. Larger studies with specific time interval of diagnosis, start and response to treatment should be taken into account when the levels are checked to ascertain the changes in isoenzymes with regard to clinical condition and stage of disease. Study of pattern at start of treatment and with remission could give a better picture of isoenzymes. Further studies in this area may suggest the role of LDH as a prognostic factor and help in correlating with survival status.

CONCLUSION

All hematological malignancies had increase in LDH 1 with the exception of AML patients who had increase in LDH 4. The increase in LDH 1 was seen in ALL, CML, CLL, lymphomas and multiple myeloma, while LDH 2

was decreased in ALL, AML, lymphoma and MM. LDH 1 isoenzyme is most prominent to be raised in malignancies. LDH 2 isoenzyme forms the major subgroup of LDH enzyme levels and it's decrease is more evident in malignancies.

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