Original Research Article

Utility of Serum Lactate Dehydrogenase and Uric Acid Concentrations as Prognostic Indices for Leukemia Patients under Chemotherapy in a Tertiary Care Hospital of Assam

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ABSTRACT

Background: A rapid evaluation and initiation of appropriate treatment is necessary in leukemia patients because of its overwhelming impact on prognosis in terms of achieving complete remission and a better quality of life. In addition to hematological and bone marrow examination, biochemical test such as serum lactate dehydrogenase (LDH) activity and uric acid concentration have gained importance in monitoring the prognosis of leukemia, especially during the phase of treatment.
Aim: So the study was being undertaken in order to evaluate serum LDH activity and uric acid concentrations before and after chemotherapy both in terms of clinical significance as well as in terms of possible use as cheaper biochemical parameters of neoplastic activity in leukemic patients.
Methods: Thirty newly diagnosed cases of leukemia, irrespective of their age were selected on the basis of clinical history, examination and relevant investigations and equal numbers of controls taken. Serum LDH and Uric acid were estimated before initiation of chemotherapy and after one month of chemotherapy. Statistical analysis of the data was performed by using Microsoft Excel software.
Results: In our study, a very highly significant difference (elevation) in the mean value of serum uric acid concentration and LDH activity has been found between the leukemic patients at diagnosis and control group ($p < 0.0001$) but the difference have been substantially reduced after one month of chemotherapy.
Conclusion: We suggest that biochemical alteration of serum LDH activity and uric acid concentration can play an important role in the prognostic aspect of the disease if continuous monitoring of these two parameters is done.

Key words: Leukemia, Serum Lactate dehydrogenase, Uric acid, Assam.

INTRODUCTION

Leukemias are malignant disorders of the haematopoietic stem cell compartment, characteristically associated with increased numbers of white cells in the bone marrow and peripheral blood. [1] The word *leukemia* though literally means "white blood" but is used to describe a variety of cancers that begin in the blood-forming cells of the bone marrow. Leukemia is caused by

the mutation of the bone marrow pluripotent or most primitive stem cells and this neoplastic expansion results in abnormal, leukemic cells and impaired production of normal red blood cells, neutrophils and platelets. Leukemia is the most common malignancy among patients less than 15 years of age. [2] Leukemia can be broadly classified as acute and chronic according to the clinical course and myeloid and lymphoid according to the cell line predominantly involved in the leukemic process. [3]

The incidence of leukemias of all types in the general population is approximately 10/100000 per annum, with males being more affected than females, the ratio being about 3:2 in acute leukemia, 2:1 in chronic lymphocytic leukemia (CLL) and 1.3:1 in chronic myeloid leukemia (CML). [1] In India, Leukemia continues to be the largest contributor to cancer related mortality in children. [4] Due to the lack of any nationwide leukemia screening program, the majority of the population of India is still unaware of this blood disorder. ALL is predominantly a disease of children, with highest incidence in children between the ages of 2 and 6. ALL has a second peak incidence in the elderly population. The incidence of AML increases with age, accounting for 80% of acute leukemias in adults and for 15% to 20% of acute leukemias in children. The rate of AML is somewhat higher in males than females. [5] Chronic leukemias, both CLL as well as CML occur mainly in middle and old age. [1] The etiology of most of the cases is unknown, but previous exposure to ionizing radiation, cytotoxic chemotherapeutic agents, or benzene is the presumed causes. Several congenital diseases, such as Down syndrome, Bloom syndrome and Turner syndrome have an increased incidence of AML. [6]

Once the diagnosis of leukemia is suspected, a rapid evaluation and initiation of appropriate treatment is necessary because of its overwhelming impact on prognosis in terms of achieving complete remission or providing a better quality of life for a longer period of time. Haematological and bone marrow examination are the main parameters for the diagnosis of leukemia and also important indices for monitoring the prognosis of leukemia during and after treatment. In addition biochemical test such as serum lactate dehydrogenase (LDH) activity and uric acid concentration have side by side gained importance in monitoring the prognosis of leukemia, especially during the phase of treatment. LDH, a pyridine-linked enzyme found in virtually all animal and human tissue, 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 lactate to pyruvate during gluconeogenesis. Its concentration is highest in liver followed by skeletal muscle, heart and kidney. [7] LDH activity is present in all cells of the body and is invariably found in the cytoplasm of the cell. Leakage of the enzyme from even a small mass of damaged tissue increases the serum activity of LDH to a significant extent. [7] In cancers of haematopoietic system mainly leukemia, LDH activity is increased and there is a good correlation between serum LDH and leukemia in terms of disease activity. In human, uric acid is the major product of the catabolism of the purine nucleosides adenosine and guanosine. Purines from catabolism of dietary nucleic acid are converted to uric acid directly. The bulk of purine excreted as uric acid arise from degradation of endogenous nucleic acids. [8]

Serum uric acid is also raised in patients with haematopoietic malignancies due to increase in cell turnover of malignant

cell population leading to increased purine catabolism, ultimately resulting in the elevation of serum uric acid level. Hence, serum uric acid and LDH estimations, which are easily available and cost effective, have gained considerable appreciation as valuable prognostic markers of leukemia. So, in order to evaluate serum LDH activity and uric acid concentrations before and after chemotherapy both in terms of clinical significance as well as in terms of possible use as cheaper biochemical parameters of neoplastic activity in leukemic patients admitted in Assam Medical College & Hospital, Dibrugarh, the study was being undertaken. We also wanted to evaluate the utility of serum LDH activity and uric acid concentration as a prognostic index in Leukemia patients as no previous data is available regarding it in this eastern most part of the Indian subcontinent.

MATERIALS AND METHODS

The present study was undertaken in the Department of Biochemistry in collaboration with Department of Medicine and Department of Paediatrics, Assam Medical College and Hospital (AMCH), Dibrugarh, Assam from July 2011 to June 2012. After obtaining approval from Institutional Human Ethics Committee, 30 newly diagnosed patients as cases of leukemia, both male and female, irrespective of their age were selected on the basis of clinical history, examination and relevant investigations. Patients already on chemotherapy or having history of primary gout were excluded from the study. Equal numbers of age and sex matched controls from similar socio-economic background were taken. Blood samples were collected in vacutainers under all aseptic and antiseptic conditions without application of tourniquet and serum was separated by centrifugation. Different parameters were estimated on Merck Microlab 300 Semi automated

analyzer. All the reagent kits used were manufactured by Coral Clinical Systems. Serum uric was estimated by uricase method and serum LDH by Modified IFCC method.[9,10] Routine hematological examinations, serum urea and creatinine estimations were done as per standard procedures. Then chemotherapy was initiated and tests were repeated after one month of completion of chemotherapy. Statistical analysis of the data was performed by using Microsoft Excel software. A 'p' value of less than or equal to 0.05 was considered significant.

RESULTS

In our study, serum uric acid and LDH of 30 cases and equal number of controls were analysed of which 17 (56.67%) were males and 13 (43.33%) were females. Out of the 30 cases, 17 were diagnosed as CML, Nine were diagnosed as ALL and 2 cases each were diagnosed as AML and CLL (Fig.1). The male patients constitute 56.67% and the female patients constitute 43.33% of the total cases. Age distribution in different types of leukemia cases are shown in Tab.1 from where it is evident that highest numbers of cases are occurring in age group of 0-10 years (26.67%) followed by 41-50 years (23.33%) age group. When we see the distribution of serum uric acid concentration in leukemic patients before and after 1 month of chemotherapy with the control group, a very highly significant difference (elevation) in the mean value of serum uric acid concentration has been found between the leukemic patients at diagnosis and control group ($p < 0.0001$) but the difference have been substantially reduced after one month of chemotherapy (Fig.2). In the present study, it was seen that 96.6% of cases with leukemia have serum lactate dehydrogenase activity above the normal range with the mean LDH activity being 774.2 IU/L and 3.3% of cases towards the higher normal

range with the mean LDH being 406 IU/L at diagnosis (Fig.3). Here also very highly significant difference (elevation) in the mean value of serum LDH activity has been found between the leukemic patients at diagnosis and control group (p < 0.0001) which showed significant lowering after one month of chemotherapy to p<0.05. In Tab.2, mean serum uric acid concentration in different types of leukemia patients, before and after one month of chemotherapy is shown which is revealing a downward trend. Maximum rise in serum uric acid concentration before chemotherapy was seen in AML followed by CML. Likewise, mean serum LDH activity in different types of leukemia before and after 1 month of chemotherapy is shown in Tab.3 where reduction in the serum uric acid

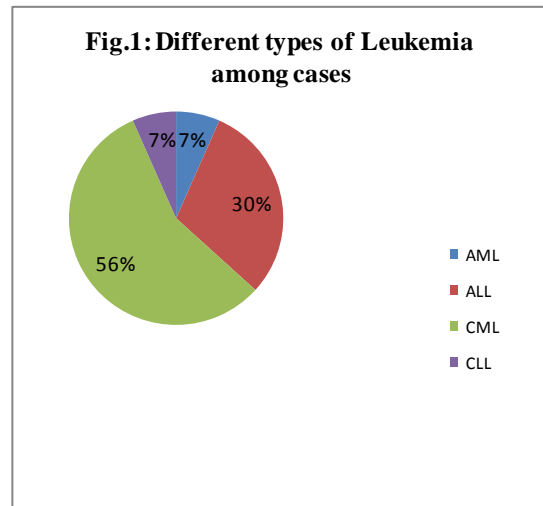concentration was seen in all types of leukemia after chemotherapy.

Fig.1: Different types of Leukemia among cases

Table 1: Age Distribution in Different Types of Leukemia

AGE GROUP (in years)	AML	ALL	CML	CLL	TOTAL Number	%
0—10	0	6	2	0	8	26.67
11—20	0	2	0	0	2	6.67
21—30	0	1	3	0	4	13.33
31—40	1	0	3	0	4	13.33
41—50	1	0	5	1	7	23.33
51—60	0	0	3	0	3	10.00
61 & Above	0	0	1	1	2	6.67
TOTAL	2	9	17	2	30	100.00

Fig.2: Distribution of Serum Uric acid concentrations in Leukemic patients and Controls

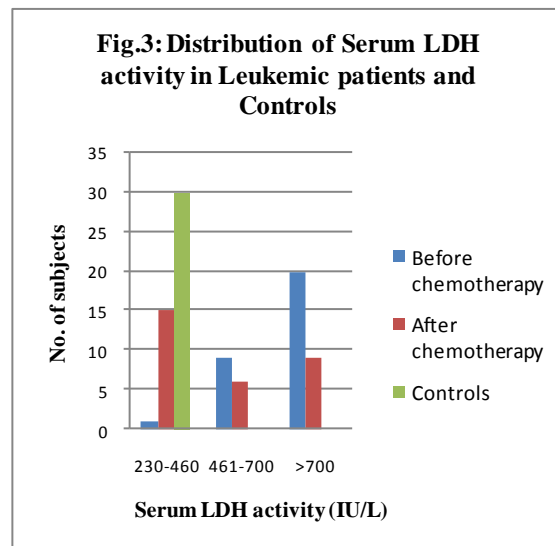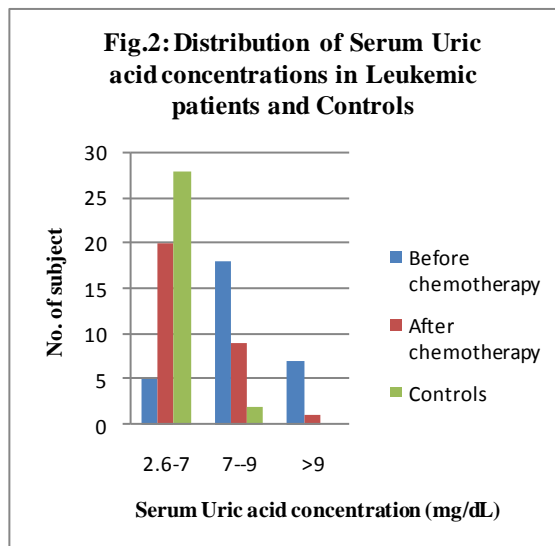Fig.3: Distribution of Serum LDH activity in Leukemic patients and Controls

Table 2: Mean Serum Uric acid Concentrations in Different Types of Leukemia Before and After 1 Month of Chemotherapy

Serum Uric Acid	TYPES OF LEUKEMIA			
	AML	ALL	CML	CLL
Before Chemotherapy (mg/dL)	9.80	7.72	8.98	6.10
After Chemotherapy (mg/dL)	8.20	6.21	6.91	5.10

Table 3: Mean Serum LDH Activity in Different Types of Leukemia Before and After 1 Month of Chemotherapy

Serum LDH Activity	TYPES OF LEUKEMIA			
	AML	ALL	CML	CLL
Before Chemotherapy (IU/L)	1058.50	655.83	821.05	436.00
After Chemotherapy (IU/L)	784.00	441.00	622.3	380.00

DISCUSSION

The present study revealed that serum uric acid concentration and LDH activity were altered in leukemia patients after chemotherapy. As per Table.1, maximum number of leukemic patients i.e. 8 patients (26.67%) were in the age group of 0-10 years followed by 7 patients (23.33%) in the age group of 41-50 years which is similar to the findings in studies done by Jacob F. *et al*, AK Siraj *et al*, S. Ghosh *et al* and Moe Wakui *et al*. [11-14] In the present study (Fig.2), it was seen that 83.3% of cases with leukemia have serum uric acid concentration above the normal range with the mean uric acid level being 8.92 mg/dL and 16.6% of cases towards the higher normal range with the mean uric acid level being 6.16mg/dL at diagnosis. The probable cause of increase serum uric acid level in the study group is due to increased nucleic acid catabolism due to increased turnover of malignant cells resulting in increased purine catabolism. The difference have been substantially reduced after one month of chemotherapy which means on completion of the chemotherapy regimen there would be statistically no significant difference between the cases and controls. So in the present study the findings were similar to the observations made by Pui C H et al, Jacob F et al, Miroljub Petrovi and Miodrag Raji. [15,11,16]

In the present study (Fig.3), it was seen that 96.6% of cases with leukemia have serum lactate dehydrogenase activity above the normal range with the mean LDH activity being 774.2 IU/L and 3.3% of cases towards the higher normal range with the mean LDH being 406 IU/L at diagnosis. The result could be explained as LDH activity is elevated due to leukemic cell lysis, or increased cellular LDH activity reflects glycolysis in the cytoplasm of malignant cells accompanied by high turnover rate. All subjects in the control group were found to be within the normal range (230-460 IU/L). A significant difference (elevation) in the mean value of serum LDH activity is still present between the leukemic patients after chemotherapy and controls ($p < 0.01$) but the difference have been substantially reduced which means on complete follow up of the chemotherapy regimen there would be statistically no significant difference between the cases and controls. These findings were similar to observations made by Farber S *et al*, Silver RT *et al*, Emad A Al-Saadoon *et al*, Hafiz MG *et al*. [17-20]

CONCLUSION

Leukemias still remains a challenge for the treating physicians, both in adults and children because of high mortality and morbidity. Early therapy may prolong the life expectancy to some extent provided the case has been detected at the earliest, investigated and treatment initiated with proper monitoring. Our study concludes that biochemical alteration of serum LDH activity and uric acid concentration can play an important role in the prognostic aspect of the disease if continuous monitoring of these two parameters is done as both serum uric acid and LDH measurement are easily available in laboratory and much cheaper parameters to assess disease progression. However, we are constrained by the smaller sample size and time limit and longer

duration studies with larger sample size might throw more light and help in better management of the leukemia patients.

REFERENCES

1. J I O Craig, D B L McClelland, C A Ludlam. Blood disorders: Functional anatomy, physiology and investigations *In* Davidson's principles and practice of Medicine. 20[th]ed. Elsevier Publications, Chapter 24, 2007:889.
2. Dario Campana, Ching-Hon Pui. Childhood Leukemia *In* Abeloff's Clinical Oncology. 4th ed. Elsevier Health, Chapter 101, 2008.
3. De Gruchy's Clinical Haematology in Medical Practice 5th ed, Wiley-Blackwell, Chapter 10, 1989:237-240
4. Arora R S, Eden T, Kapoor G. Epidemiology of childhood cancer in India. Indian J Cancer. 2009;46:264-273
5. Betty Ciesla; Acute leukemias *In* Hematology in practice. F.A. Davis Company, Chapter 11, 2007:161 and 175.
6. Douglas C Tkachuk, Jan V Hirschmann. Acute Leukemias *In* Wintrobe's Atlas of Clinical Hematology. 1st ed, Lippincott Williams & Wilkins, Chapter 2, 2007.
7. Puc CH, Dodge R K, Dahl G V *et al*. Serum lactic dehydrogenase level has prognostic value in childhood acute lymphoblastic leukemia. Blood. 1985; 66: 778-782
8. Teitz Textbook of Clinical Chemistry and Molecular Diagnostic. 4th ed, Elsevier Saunders, 2006:601, 803–805.
9. Fossati P, Prencipe L, Berti G. Use of 3,5-Dichloro- 2-hydroxybenzene-sulfonic Acid/4-Aminophenazone Chromogenic System in Direct Enzymic Assay of Uric Acid in Serum and Urine. Clin.Chem. 1980; 26(2):227-231.
10. Mathieu M, Artur Y, Aubry A, Bailly M, Braun JP, Bretaudiere JP et al. Recommendations for determining the catalytic concentration of lactate dehydrogenase in human serum at +30 °C. *Ann Biol Clin.* 1982; 40:87-164.
11. Jacob F, Reaman G H, Sposto R, Sensel MG. Treatment outcome and prognostic factors for infants with acute lymphoblastic leukemia, Journal of Clinical Oncology. 1994;17:445.
12. Siraj A K , Kamat S, Gutiérrez M I, Banavali S, Timpson G, Sazawal S et al. Frequencies of the major subgroups of precursor B-cell acute lymphoblastic leukemia in Indian children differ from the West. Leukemia . 2003; 17(6):1192–1193.
13. Ghosh S, Shinde SC, Kumaran GS, Sapre RS et al. Haematologic and immunophenotypic profile of acute myeloid leukemia: An experience of Tata Memorial Hospital. Indian J Cancer; 2003;40(2):71-76.
14. Wakui M, Kuriyama K, Miyazaki Y, Hata T, Taniwaki M, Ohtake S, et al. Diagnosis of acute myeloid leukemia according to the WHO classification in the Japan Adult Leukemia Study Group AML-97 protocol. Int J Hematol 2008;87:144–151.
15. Pui C H, Evans W B. Drug Therapy: Acute Lymphoblastic Leukemia, N Engl J Med, 1998; 339:605-615.
16. Miroljub Petrovi, Miodrag Raji. Biochemical Alterations in patients with Acute Leukaemia. Jugoslov. Med. Biochem. 2002; 21: 351– 354.
17. Farber S, Diamond L K, Mercer R D, Sylvester R F Jr., Wolff J A. Temporary Remissions in Acute Leukemia in Children Produced by Folic Acid Antagonist, 4-Aminopteroyl-Glutamic Acid (Aminopterin). N Engl J Med, 1948; 238:787-793.
18. Silver RT, Woolf SH, Hehlmann R, et al. An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: developed for the American Society of Hematology. Blood 1999; 94:1517-36.
19. Emad A Al-Saadoon, Lamia M Al-Naama, Janan K Hassan. Serum Lactate Dehydrogenase (LDH) Activity in

Children with Malignant Diseases. Bahrain Medical Bulletin 2003; 25(2):71-73.

20. Hafiz M G, Rahman M M, Mannan M A. Serum lactate dehydrogenase as a prognostic marker of childhood acute lymphoblastic leukemia. Mymensingh Med J. 2008;17(2):169-173.

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