Serum Lactic Dehydrogenase (LDH) Levels in Acute Leukemia: Marked Elevations in Lymphoblastic Leukemia

By Abraham Kornberg and Aaron Polliack

Serum total lactic dehydrogenase (LDH) levels were examined in 42 patients with acute leukemia, 9 patients with chronic myeloid leukemia, 6 of them in blast crisis, and 53 patients with lymphoma and other lymphoproliferative disorders. The mean range of serum LDH levels in Hodgkin's and non-Hodgkin's lymphoma was 402 ± 210 IU/liter and 313 ± 113 IU/liter, while that of patients with nonmalignant disorders was 308 ± 210 lU/liter. In acute nonlymphoblastic leukemia (ANLL), the range was 126–684 IU/liter (mean value of 413 ± 146 IU/liter). In 6 of the patients (11.3%) with lymphoma and in 6 cases (26.8%) with ANLL, the LDH levels were above 500 IU/liter. None of these patients had levels over 900 IU/liter. Patients with acute lymphoblastic leukemia (ALL) had a range of 402–3582 lU/liter (mean value of 1669 ± 1038 lU/liter). In 15 of the 19 patients (78.9%) with ALL, serum LDH values were above 900 IU/liter. In addition, 3 patients with chronic myeloid leukemia (CML) in blastic crisis had levels of 970–1940 IU/liter. One of these 3 patients had lymphoblastic crisis, while the second case responded clinically to vincristine and prednisone, but was not regarded as ALL. The differences in serum LDH levels between ALL and ANLL are statistically significant (p < 0.001). It appears that markedly elevated serum LDH levels in acute leukemia are suggestive of ALL, and that in individual patients, the LDH levels were correlated with the number of blasts during remission and relapse.

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 workers, in both human and animal tumors. Elevated LDH levels are encountered in neoplastic tissues as well as in the serum of patients with a variety of epithelial tumors. In non-Hodgkin's lymphoma, particularly Burkitt's lymphoma, the serum LDH levels are elevated in many patients, but there does not appear to be a good correlation between increased LDH levels and specific types of solid tumors. In animal and human leukemias, elevated LDH levels have frequently been observed. In addition, there appears to be a good correlation with disease activity and tumor mass, but until now, elevated levels have not been shown to correlate with the type of leukemia.

Recently, we have studied total serum LDH levels in 42 patients with acute leukemia. The results indicate that LDH levels are moderately elevated in many cases of acute leukemia, irrespective of their cell type. However, markedly elevated levels were recorded in the majority of patients with acute lymphoblastic leukemia (ALL) and in blastic crisis of chronic myeloid leukemia, but not in any of the patients with acute nonlymphatic leukemia (ANLL). These results suggest that markedly elevated serum LDH levels are more indicative of ALL than ANLL.

MATERIALS AND METHODS

Enzyme Assay

Serum LDH levels were determined according to the method of Morgensten et al. The determination was done on the day of admission to the hospital and in all cases before chemotherapy was started. In four patients with ALL, isoenzymes were determined.

Patient Material

Serum LDH levels were assayed in 42 patients with acute leukemia. Nineteen patients had ALL, including 2 patients with Burkitt's lymphoma (11 males, 8 females), and 23 patients had ANLL (20 patients with AML, 2 patients with monoblastic leukemia, and 1 patient with promyelocytic leukemia; 11 males, 12 females). In addition, sera from 9 patients with CML, 6 of them in blastic crisis, were examined (7 males, 2 females). The range of age for the ALL group was 11–70 yr (mean 26 yr), ANLL group 17–77 yr (mean 46 yr), and CML group 24–62 yr (mean 34 yr). The control material included 53 patients with malignancies: Hodgkin's and non-Hodgkin's lymphoma, chronic lymphatic leukemia (CLL), and multiple myeloma (MM), and 30 patients with nonmalignant disorder (iron-deficiency anemia, systemic lupus erythematosus—SLE, idiopathic thrombocytopenic purpura—ITP, aplastic anemia, and thrombophlebitis) (Table 1). Cases with signs of hemolysis and liver damage were excluded from this series.

Classification of Leukemia

All cases of acute leukemia were classified into two main categories (ALL and ANLL), primarily on the basis of light microscopy and cytochemistry, and in the more difficult cases by cell surface markers and ultrastructure. The following cytochemical stains were performed: peroxidase, periodic acid Schiff (PAS), sudan black, nonspecific esterases with and without fluoride inhibition, As-D chloroacetate esterase, acid phosphatase, and oil red 0. In general, cases were classified as ALL if cells were negative for peroxidase, sudan black, and esterases, while some were positive for paranuclear acid phosphatase, PAS, and oil red 0. ANLL was diagnosed if cells were positive for either sudan black, peroxidase, or esterases and negative for oil red 0, PAS, or paranuclear acid phosphatase. A proportion of ALL cases were examined for the following surface markers: FC receptor, C1 receptors, surface...
immunoglobulin, E-rosettes, and T-antigen using anti-T-cell antisera. In some cases, transmission and scanning electron microscopy were performed to assist in definition of the cell type. Statistical analysis was done according to Student's t test.

RESULTS

The serum LDH levels in all the cases of acute leukemia and from the control groups are shown in Fig. 1. The number of patients in each group, the range of LDH levels, and the mean values are summarized in Table 1.

The normal range of total serum LDH in the Hadassah University Hospital is 100–500 IU/liter. This is reflected in the nonmalignant disorders, where the range was 180–491 IU/liter (mean value was 308 ± 74 IU/liter). Among the malignant disorders, sera from patients with Hodgkin's and non-Hodgkin's lymphoma displayed a range of LDH levels from 226 to 898 (mean 402 ± 210 IU/liter), and 160–590 (mean 313 ± 113 IU/liter), respectively. In 6 of the above 38 patients, LDH levels were above 500 IU/liter (588–898 IU/liter). In all the patients with MM and CLL, the levels were less than 500 IU/liter. In ANLL, the range of serum LDH was 126–684 IU/liter (mean value 413–146). In 6 ANLL patients, LDH levels were above 500 IU/liter, but no patient had levels above 900 IU/liter. The range of levels in ALL was 402–3582 IU/liter (mean value of 1661 ± 1038 IU/liter). In 15 of the 19 ALL patients (78.9%) the values were above 900 IU/liter, while in only 4 patients the levels were below 500 IU/liter. In three of the patients with CML, all in acute blastic metamorphosis, the LDH levels were elevated (range 970–1940 IU/liter). One of these cases had a lymphoblastic crisis, while the second was undifferentiated in type but responded to vincristine and prednisone. Isoenzymes were determined in only 4 ALL patients, and in all these cases both isoenzymes 2 and 3 were found to be elevated; however, isoenzyme 3 was more markedly elevated than isoenzyme 2 in these patients.

There is no statistically significant difference in the serum LDH levels among the patients with ANLL leukemia and the various control groups (p > 0.05). However, the differences in LDH levels between the ALL patients and all the other groups were statistically significant (p < 0.001).

On initial admission, no correlation existed between the absolute number of circulating ALL blasts and the serum LDH levels (Fig. 2). This phenomenon may be explained by the possibility that elevated serum LDH levels may relate more to total leukemic cell mass than to the numbers of circulating blasts. However, in individual patients with ALL, good correlation was found during cytotoxic treatment, remission, and relapse. This is clearly demonstrated in Fig. 3 and 4.

Table 1. Range and Mean Values of Serum LDH in 125 Patients With Acute Leukemia, Lymphoma, and Nonmalignant Disorders

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>No. of Patients</th>
<th>Range of Serum LDH Levels (IU/Liter)</th>
<th>Mean ± SD Serum LDH levels (IU/Liter)</th>
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</thead>
<tbody>
<tr>
<td>ALL</td>
<td>19</td>
<td>402–3,582</td>
<td>1,669 ± 1,038</td>
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<tr>
<td>ANLL</td>
<td>23</td>
<td>126–684</td>
<td>413 ± 146</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>15</td>
<td>226–898</td>
<td>402 ± 210</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>23</td>
<td>160–590</td>
<td>313 ± 113</td>
</tr>
<tr>
<td>CLL</td>
<td>9</td>
<td>254–444</td>
<td>335 ± 69</td>
</tr>
<tr>
<td>MM</td>
<td>6</td>
<td>184–488</td>
<td>317 ± 114</td>
</tr>
<tr>
<td>Nonmalignant disorders</td>
<td>30</td>
<td>180–491</td>
<td>308 ± 74</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>5</td>
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<tr>
<td>Thrombophlebitis</td>
<td>8</td>
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<tr>
<td>Aplastic anemia</td>
<td>4</td>
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<tr>
<td>SLE</td>
<td>6</td>
<td></td>
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<td>ITP</td>
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ACUTE LYMPHOBLASTIC LEUKEMIA

ACUTE NON LYMPHOBLASTIC LEUKEMIA

from data obtained in two patients. Serum vitamin B₁₂ and folic acid levels were available in 12 of the 15 patients with elevation of serum LDH. No cases showed megaloblastic changes or vitamin B₁₂/folic acid deficiency. (Vitamin B₁₂ recorded from 360 pg/ml to 4000 pg/ml; folic acid 160–320 ng/ml.)

Lactic dehydrogenase occurs in different cell systems in the form of five isoenzymes, LDH-1–5.³⁴ The production of LDH-1 and LDH-5 is controlled by the action of two genes, while the intermediate fractions (LDH-2–4) are considered hybrid forms of LDH-1 and LDH-5, formed by association of the peptides making up the tetramers of LDH-1 and 5. Their concentration is determined by the activity of the two alleles controlling LDH-1 and LDH-5. Different LDH isoenzymes are found in various tissues, and during the development of embryonic organs, a shift in the LDH isoenzymes pattern occurs. Accordingly, the isoenzyme content of fetal and adult cells of the same type is different. In hematopoietic tissues, erythrocytes contain mainly LDH-1–3, while LDH-5 is the predominant isoenzyme in proerythroblasts and early normoblasts.³⁰,³⁴,³⁵ Maturing cells of the granulocytic and lymphocytic series contain mainly isoenzymes 1–3, but at the blast stage, LDH-1 and -2 are decreased, resulting in a predominance of LDH-3. Mature peripheral blood lymphocytes and granulocytes are quite similar with respect to their LDH isoenzyme content, and both cell types contain mainly LDH-5. In normal human plasma, isoenzymes 1 and 2 predominate, but the sources of this activity have as yet not been clearly established. In conditions with tissue damage and rapid cell turnover, such as
malignant neoplasia, the serum LDH may rise, and the isoenzyme distribution usually reflects that of the damaged organ and cells.

In the present study, serum total LDH levels were moderately elevated in 6 of 23 patients (26%) with ANLL and in 6 of 38 patients (16%) with malignant lymphoma. None of these patients had levels above 900 IU/liter. In ALL, LDH levels were markedly elevated. In 15 of 19 patients (79%), the levels were above 900 IU/liter, and in some cases, could be used as a rough indicator of the total tumor mass. Furthermore, when these levels in ALL were compared to those obtained for other groups, they were found to be statistically significant. Among the CML patients, the enzyme levels were elevated in one patient with lymphoblastic crisis and in another case of undifferentiated type crisis who responded to vincristine and prednisone. In our opinion, marked elevations of LDH are highly suggestive of acute leukemia of lymphoblastic type. Recently, markedly raised LDH levels have been recorded in rare patients with acute megakaryoblastic leukemia, but no cases of this nature were studied in the present series.

Our results are similar to those obtained by Stuart et al., Sactor et al., and other authors who have shown increased LDH activity in isolated lymphoblasts and in the serum of patients with ALL and in animals with transplantable lymphatic leukemia. In patients with Burkitt’s lymphoma, the serum LDH levels are frequently elevated above 700 IU/ml, and LDH levels were found to correlate well with the tumor mass. In contrast to the above data and the findings of this study, Bierman et al. reported elevated levels in 47 of 54 patients with lymphatic leukemia and in all 36 patients with myeloid leukemia. They also recorded elevated LDH levels in 86% of patients with malignant lymphoma. However, from their study, the distinction between acute and chronic leukemias is not clear. In this respect, it is of interest to record that other authors have demonstrated increased LDH levels in primary and transplanted induced murine myeloid leukemias.

Increased cellular LDH activity reflects a shift towards anaerobic metabolism and increased glycolysis in the cytoplasm of malignant cells accompanied by a high turnover rate. The variations in the levels of serum LDH encountered in different malignant neoplasms and the markedly elevated levels found in patients with ALL may reflect basic differences in cell proliferation and turnover in these disorders.

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