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VALUATION OF LEVELS OF SERUM FERRITIN IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Abstract:
Background: *Acute lymphoblastic leukemia (ALL) is the most common malignant neoplasm of childhood. Although an increase in serum ferritin is known with many forms of malignant tumors, the pattern of elevation in different stages of ALL has not yet been elucidated.*
Objectives: *To evaluate serum ferritin, uric acid and LDH levels in patients with acute lymphoblastic leukemia.*
Materials and Methods: *This is a case-control study conducted in the Medicine department of Mayo Hospital Lahore in Collaboration with Oncology department for one-year duration from May 2019 to May 2020. A total of 160 people was enrolled in the study, including 80 ALL patients as cases; and sexually matched, 80 healthy individuals as controls. All test results were statistically analyzed using the Social Sciences Statistical Package (SPSS) version 20.0.*
Results: *The study involved 160 people, 80 patients with ALL, 42 of whom (52.5%) were men, and 38 (47.5%) were women. The mean age in the group of patients was 17.6 ± 5.6 years. The control group consisted of 80 healthy people who were matched in terms of age (17.8 ± 12.1) and sex (52.5% men, 47.5% women) to the case group. Among patients with ALL, statistically significant positive correlations were found between the number of blasts: serum ferritin ($r = 0.735$, $p < 0.0001$), uric acid ($r = 0.618$, $p < 0.0001$) and LDH ($r = 0.570$, $p < 0.0001$).*
Conclusions: *ALL was associated with elevated serum ferritin levels. Serum ferritin was significantly correlated with different disease stages and showed a positive linear correlation with the concentration of uric acid, LDH and serum blasts, therefore the determination of serum ferritin could be used as prognostic markers of ALL.*
Key words: *serum ferritin, acute lymphoblastic leukemia, blood.*

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INTRODUCTION:

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, affecting about 2-4 in 100 children under 15 years of age. There has been a remarkable development in the outcomes of ALL patients over the past 40 years[1-2]. Prior to the introduction of effective cancer chemotherapy, ALL was equally fatal some 40 years ago, with most children only surviving 2-3 months after diagnosis. Currently, however, approximately 60% of children with this disease are in continuous complete remission 5 years after initial diagnosis; most of these children are considered cured. The clinical onset of ALL is most often acute, although a small percentage of cases can evolve insidiously within a few months. The presented symptoms and signs correlate with the load on leukemia cells and the degree of bone marrow replacement, which leads to cytopenia[3-4]. The most common symptoms are fever (due to leukemia or a secondary infection secondary to neutropenia), fatigue and lethargy (due to anemia), bone and joint pain, and hemorrhagic diathesis (related to thrombocytopenia). T-cell precursor ALL / LBL patients often have a mediastinal mass with or without associated pleural effusions, which can lead to respiratory failure and other symptoms of superior vena cava syndrome. Typical extramedullary sites of involvement include the lymph nodes, liver, spleen, and meninges, while less commonly, ALL can infiltrate orbital tissues, testes, tonsils, and tonsils[5-6]. Rarely, patients presenting with B-LBL may show cutaneous lesions with lymphadenopathy in the head and neck area or discrete bone changes. The most common laboratory abnormalities in ALL include anemia, thrombocytopenia, neutropenia, and leukopenia or leukocytosis, with hyperleukocytosis (> 100-109 / L) present in approximately 15% of children. Other common laboratory abnormalities include elevated serum uric acid and lactose dehydrogenase levels, correlating with tumor weight and tumor lysis rate[7-8]. Massive cell death and the breakdown of the nucleus of the malignant colon generate large amounts of the nucleic acid of these purines (adenine and guanine), which are converted to uric acid by purine degradation, leading to hyperuricemia. An increase in LDH is usually seen in tumor lysis syndrome, possibly due to anaerobic glucose metabolism. Serum LDH is often elevated in lymphoproliferative diseases, in patients with non-Hodgkin's lymphoma. LDH is of prognostic value and is commonly used to evaluate treatment response and monitor tumor recurrence. Although iron is an essential micronutrient for DNA synthesis, besides the metabolism of respiratory and oxidative cells, its pro-oxidative properties can cause carcinogenicity. Free iron can catalyze the formation of mutagenic hydroxyl radicals, which in turn can cause increased oxidative stress, DNA damage, and activation of oncogenes. Iron also suppresses the host's defenses, thereby allowing cancer cells to proliferate, and acts as a nutrient for the unrestricted proliferation of cancer cells. Iron was carcinogenic in animal models, and in several studies iron stores were positively associated with the risk of certain human cancers, including colon and liver[9]. Heme iron is of particular concern given that the body is still absorbing it even when its stores are sufficient. Patel et al. Studied patients with various hematological malignancies to determine the relationship between changes in serum ferritin concentration and the clinical status of patients. It was found that patients with Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, chronic myeloid leukemia blast crisis, acute myeloblastic leukemia, and ALL had significantly elevated serum ferritin levels. Serum ferritin levels reflect acute phase reactions and are usually associated with iron storage. Other recent research suggests that ferritin is a substitute for advanced disease and has an impact on relapse, as elevated serum ferritin levels predict overall and relapse-free survival after autologous stem cell transplant in lymphomas. In untreated ALL patients, mean serum ferritin levels were approximately 15 times higher than normal in this age group. During chemotherapy the levels of circulating ferritin were higher than in the period before treatment. There was no correlation between the concentration of ferritin and the duration of remission in patients still receiving chemotherapy. The increase in circulating ferritin during chemotherapy may be due to the increased release from damaged leukemia cells. It is possible that chemotherapy also damages other ferritin-containing cells, but the lack of correlation with serum transaminase activity makes it unlikely that liver parenchymal cells are an important source. Similarly, the lack of correlation between elevated serum ferritin and the amount of blood transfused, unlike in aplastic anemia, makes it unlikely to be due to increased stores. Low serum ferritin levels found in long-term ALL survivors suggest that ferritin levels may be a useful predictor of disease recurrence and a prognostic symptom[10]. Acute lymphoblastic leukemia is the most common malignant tumor in children. Treatment involves the introduction of chemotherapy for a long time. Increased prognosis requirements have emerged during treatment to ensure complete elimination of the malignant clone and avoid excess chemotherapy. It is known that cytogenetics was so expensive that we analyze serum ferritin as a prognostic factor and its relationship to tumor severity by its correlation with percent blasts and serum uric acid and lactate dehydrogenase levels. To our knowledge, there is little research into this type of cancer; The aim of the present study is to

provide more evidence on the relationship between serum ferritin and ALL.

MATERIALS AND METHODS:

This is a case-control study conducted in the Medicine department of Mayo Hospital Lahore in Collaboration with Oncology department for one-year duration from May 2019 to May 2020. A total of 160 people was enrolled in the study, including 80 ALL patients as cases; and sexually matched, 80 healthy individuals as controls. sample size was calculated according to the basic formula on the sample size. People who received iron supplementation or took medications that affect iron metabolism were excluded from this study. Oral consent was obtained from all subjects or their guardians prior to study inclusion. A venous blood sample (5 ml) was collected from each subject with aseptic precautions from a vein in the arm. Of which 2.5 ml was placed in an EDTA tube and used immediately for blood count, blood smear preparation and serum ferritin determination. The remaining 2.5 ml was placed in a heparinized tube and used to evaluate the serum uric acid concentration and LDH. Blood mixed with EDTA was used for complete blood counts by an automated hematology analyzer (Sysmex XT-2000I-Japan) within 1 hour of collection to minimize variation due to aging of the specimen. For the examination of thin blood spots of PBP 2 stained: one with Diff Quick staining from RAL and the other with MGG, another smear was also made and stained with SBB. The remaining blood in EDTA was centrifuged at 3200 rpm for 3 minutes to obtain plasma, and the obtained plasma was then used to determine the serum ferritin concentration by electrochemiluminescence immunoassay using the Cobas e411 automated clinical chemistry analyzer (Roche-Germany). Heparinized blood was centrifuged at 3200 rpm for 3 minutes, and the serum was collected in 1.5 ml Eppendorf tubes and stored at (2-8 ° C) for a maximum of 7 days. Serum uric acid and LDH levels were then measured with a Cobas c311 automated clinical chemistry analyzer (Roche-Germany). Statistical analysis was performed using the Social Science Statistical Package (SPSS) version 20.0. Descriptive statistics were used to summarize the characteristics of the studied population. The mean and standard deviation of the numerical variables (age, blood count parameters, blast count, uric acid concentration, serum ferritin and LDH levels) were calculated. An independent sample T-test was used to compare serum ferritin levels between patients and controls. Pearson's correlation was used to investigate the correlation between serum ferritin and other variables (uric acid, LDH, and blast count). The analysis of variance was used to compare the serum ferritin levels between the groups of patients depending on the severity of ALL using one-way ANOVA test. P <0.05 was considered statistically significant in all tests.

RESULTS:

160 people took part in this study, 80 patients with ALL, among whom 42 (52.5%) were men and 38 (47.5%) were women with an average age of 17.6 ± 5.6 years, and 80 healthy people statistically matched in terms of age (17.8 ± 5.6) 12.1) and sex (52.5% men, 47.5% women) as a control group. The hematological parameters in the group of cases show a significant decrease in hemoglobin, the number of red blood cells and red blood cell indices, as well as thrombocytopenia compared to the control group. While the total white blood cell count has increased dramatically and the dominance of blast cells indicates acute disease (Table 1).

Table 1 Mean value of blood count parameters

Variables	RBCs (× 10^{12}/l)	Hb (g/dl)	PCV (%)	PLts (× 10^9/l)	WBCS (× 10^9/l)	Blast count (× 10^9/l)	Blast (%)
Case Group	2.9	8.2	25.8	54.4	157.1	151.4	87.6%
Control Group	4.9	13.4	40.0	268.2	7.0	0.0	0.0%

Mean serum uric acid, LDH and ferritin levels were elevated in the group compared to the control group (Table 2), and the correlation of blasts with ferritin, uric acid and LDH shows a positive linear correlation using the Pearson correlation coefficient p <0.05 (Table 3).

Table 2 Mean value of uric acid, LDH and serum ferritin

Variables	Uric Acid (mg/dl)	LDH (U/L)	Ferritin (mg/l)
Case Group	7.4	699.0	510
Control Group	4.5	94.2	245

Table 3 Correlation of blast cells count with serum uric acid, LDH and ferritin levels

Variables	Mean value	Blast cells count (× 10^9/l)	Pearson correlation (r)	p-value
Uric Acid (mg/dl)	7.4	151.4	0.604	<0.0001
LDH (U/L)	699.0	151.4	0.783	<0.0001
Ferritin (µg/l)	510.0	151.4	0.735	<0.0001

The correlation of serum ferritin levels between cases and controls shows a significant difference when statistically analyzed using an independent sample T-test ($p < 0.05$) (Table 4).

Table 4 Correlation of serum ferritin levels between cases and controls

Variables	Case Group	Control Group	p-value
Serum Ferritin (µg/l)	510	245	<0.05

Serum ferritin concentrations correlate positively with serum uric acid concentrations ($r = 0.618$, $p < 0.0001$) (Table 5). Of the 80 ALL patients, there were 52 early stage (65%) patients who were newly diagnosed with acute lymphoblastic leukemia, have increased TWBC and blasts compared to other stages, and have the highest serum uric acid levels, LDH, and ferritin.

Table 5 Correlation of serum levels of ferritin with serum levels of uric acid and LDH

Variables	Mean value	Serum Ferritin (µg/l)	Pearson correlation (r)	p-value
Uric Acid (mg/dl)	7.4	510	0.618	<0.0001
LDH (U/L)	818.0	510	0.570	<0.0001

There were 21 patients (26.3%) in relapsing stage with moderate increases in TWBC, blasts, uric acid, LDH, and serum ferritin. The remaining 7 patients (8.8%) were in remission, clinical status and hematological parameters were normal or near normal (Table 6).

Table 6 Frequency and the mean value for (TWBCs, blast, uric acid, LDH, and ferritin) within the different stage of the disease

Stage	Frequency (%)	TWBCs (× 10^9/l)	Blast (× 10^9/l)	Uric acid (mg/dl)	LDH (U/L)	Ferritin (µg/l)
Early	52 (65.0%)	432.7	216.4	10.3	1280.0	834.6
Recurrent	21 (26.2%)	48.4	39.2	7.6	624.0	497.8
Remission	7 (8.8%)	11.6	5.2	4.4	194.1	200.0

Serum ferritin levels were significantly elevated in early stage patients (mean = 834.6 µg / L) compared to relapses (mean = 497.8 µg / L) and remission (mean = 200 µg / L) using unidirectional ANOVA ($p < 0.05$) (Table 7).

Table 7 Difference in serum ferritin levels within three ALL groups

Variables	Early	Recurrent	Remission	p-value
Serum Ferritin (µg/l)	834.6	497.8	200	<0.05

DISCUSSION:

Acute lymphoblastic leukemia is a childhood cancer and accounts for over 50% of leukemias in this age group. In recent years, increasing emphasis has been placed on iron levels and iron chelator in leukemic tumors, such as the cytotoxic effect of antiproliferative agents and induced cell apoptosis, assuming that iron deficiency can control the proliferation of various cancer cells and induce apoptosis. In this study, there was a significant increase in serum ferritin in patients with acute lymphoblastic leukemia compared to healthy subjects, and this is in line with a previous study by Jain et al, which evaluated 260 ALL patients, med ferritin was 1081 with significantly higher incidence of LDH[11]. Another study by Zhang et al., In which they reported several cases with different types of cancer, found elevated serum ferritin levels due to increased transferrin receptors in a malignant leukemic cell clone, and an increase in the rate of cell destruction made ferritin carry and increase serum levels, these results were also in line with the studies by Aulbert and Schmidt[12-13]. Even so, it does not agree with the study by Chua et al, which concluded that serum ferritin was not associated with cancer risk or death from cancer,

these differences may be due to differences in race, sample size, and serum measurement methods. Our study also found that variability in serum ferritin levels at different stages of the disease, with peak elevations in early stage patients and normal levels in patients in clinical remission, also had a direct positive correlation with serum uric acid, LDH, WBC count, and blasts, a study by Jain et al and Zhang et al also agree with our results, although there is confusion with the study by Ahlawat et al which found that there was no correlation between serum ferritin and total blood cell count blasts and peripheral blood blasts, and this disagreement may be due to differences in race, sample size, and the method used to measure serum ferritin[14-15].

CONCLUSIONS AND RECOMMENDATIONS:

Serum ferritin levels in patients with early and relapsed acute lymphoblastic leukemia are significantly elevated, while in patients in clinical remission it drops to normal levels. Thus, measuring and monitoring changes in serum ferritin levels can be helpful in the easy and simple assessment and prognosis of disease in these patients.

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