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MEASUREMENT OF FASTING BLOOD SUGAR, SERUM TOTAL PROTEIN, SERUM ALBUMIN, SERUM TOTAL BILIRUBIN, SERUM DIRECT BILIRUBIN, AND LIVER FUNCTION PARAMETERS FOR CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. Author FTOAJ designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SFH and RMAE managed the analyses of the study. All authors read and approved the final manuscript

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ABSTRACT

Leukemia is a common malignancy of childhood. Leukemias are group of malignant disorders of the haematopoietic tissues that are characteristically associated with increased numbers of leucocytes in bone marrow and/or peripheral blood. The aetiology of leukemia is unknown but several lines of evidence do suggest that the disease is a result of interactions between several factors for example: viral infections, ionizing radiations, chemicals and genetic factors. The incidence of ALL varies, and depends on age, sex and race. Antineoplastic agents (cytotoxic drugs) are used in the treatment of malignant diseases when radiotherapy and surgery are not possible or they are not effective. This study aims to evaluate some of biochemical parameters in children with Acute Lymphoblastic Leukemia. The results indicated that the value of parameters tested varies according to type of test (i.e. some higher than normal, some less than normal).

Matrials & Methods: Eighteen pediatric acute lymphoblastic leukemia children were included in this study. All were subjected to γ-tocopherol, methotrexate, vincristine, and 6-mercaptopurine chemotherapy treatment. Serum fasting glucose, total bilirubin, direct bilirubin, total protein, albumin, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase levels were measured using autoanalyser device.

Results: Of eighteen pediatric patients, two (11.11%) were hypoglycemic (22.00±1.00mg/dL), two (11.11%) with high direct bilirubin (0.50±0.00mg/dL), six (33.33%) with low total protein (3.83±0.85gm/dL), eight (44.44%) with low albumin (2.47±0.41gm/dL), four (22.22%) with low alkaline phosphatase (20.50±11.83U/L), six (33.33%) with high alanine aminotransferase (136.66±37U/l)., and ten (55.56%) with high aspartate aminotransferase (238.60±39.15IU/L).

Conclusions: malignancy of disease and chemotherapy treatment negatively affected biochemical levels included in this study, liver function, and nutritional status of patients.

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Keywords: Acute lymphoblastic leukemia; children; liver function; malnutrition.

1. INTRODUCTION

Leukemia is the notably common malignancy of childhood and is responsible for a third of childhood malignancy deaths. It can be defined as a neoplastic disease that includes the blood forming stem cells of the bone marrow, lymph nodes, and spleen. Acute lymphoblastic leukemia (ALL) accounts for 75% of the leukemia cases and is curable in 80% to 85% of the patients [1]. The incidence of acute lymphoblastic leukemia (ALL) differs considerably according to race and ethnic group. Childhood acute lymphoblastic leukemia (ALL) grows more frequently in boys than in girls (male: female ratio, 55% to 45%) [2]. Several genetic factors are combined with an elevated risk of acute lymphoblastic leukemia (ALL)[3] . Few environmental risk factors are correlated with acute lymphoblastic leukemia (ALL) in children. Increased rates of the disease have been bound to exposure to radiation and certain chemicals, but these associations illustrate only a very few minority of cases. Acute lymphoblastic leukemia (ALL) can be of B-cell precursor or T-cell lineage[4]. The cell-surface and cytoplasmic expression of markers of lineage (immunophenotype) classifies childhood acute lymphoblastic leukemia (ALL) into precursor B-cell (85%) or T-cell(15%) subgroups that are reminiscent of normal stages of lymphoid maturation. Many mutations that are bound to leukemogenesis target genes that regulate normal B-cell or T-cell differentiation, blockng differentiation[5].

Acute lymphoblastic leukemia (ALL) protocols involve an induction regimen with three or four anti-leukemic remedies followed by several months of consolidation therapy. Then maintenance therapy is given until two to three years from diagnosis, the longer duration being given to boys due to their inferior prognosis with shorter therapy [6].

Malnutrition represents a principal problem in children suffering from cancer [7,8]. Nutritional status can be defined by albumin and total protein [9].

The liver is a large, complex organ that is better designed for its significant role in carbohydrate, fat, and protein metabolism [10]. It is the site where waste products of metabolism are detoxified through processes such as amino acid deamination, which produces urea [11]. It is responsible for synthesizing and secreting bile and synthesizing lipoproteins and plasma proteins[12]. It maintains blood glucose concentration by taking up and storing glucose as glycogen (glycogenesis), breaking this down to glucose when needed (glycogenolysis) and synthesizing glucose from non-carbohydrate sources such as amino acids (gluconeogenesis) [13].

Abnormal liver enzyme concentrations may signal liver damage or alteration in bile flow [14]. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are enzymes that catalyze the transfer of α-amino groups from aspartate and alanine to the α-keto group of ketoglutaric acid to generate oxalacetic and pyruvic acids respectively, which are significant contributors to the citric acid cycle [15]. Both aminotransferases are concentrated and accumulated in the liver[16].

Alkaline phosphatase (ALP) is an enzyme that transports metabolites across cell membranes . Liver and bone diseases are the most common causes of pathological concentrations of alkaline phosphatase (ALP) levels, although alkaline phosphatase (ALP) may originate from other tissues such as the placenta, intestines or kidneys, or from leukocytes .Hepatic alkaline phosphatase (ALP) is found on the surface of bile duct epithelia.

Bilirubin is the product of hemoglobin catabolism within the reticuloendothelil system. Heme breakdown specifies the formation of unconjugated bilirubin which is then transported to the liver. In the liver conjugated bilirubin is synthesized and excreted into the bile. In healthy people, bilirubin is actually missed from serum mainly because of the rapid process of bile secretion. Levels elevate when the liver has lost at least half of its excretory capacity [17].

This study aimed to measure serum levels of fasting glucose, total protein, albumin, total bilirubin, direct bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase and to investigate their relation with liver function and nutritional status of pediatric patients with acute lymphoblastic leukemia (ALL). Also this study investigated the impact of chemotherapy treatment on these biochemical tests and thereby showing their effect on body function for pediatric acute lymphoblastic leukemia patients.

2. MATERIALS AND METHODS

2.1 Study Cases

The study included eighteen pediatric patients suffering from acute lymphoblastic leukemia (ALL) attended the Central Child Hospital in Baghdad,

Table 1. Reference pediatric levels for biochemical tests used in this study

Levels / Biochemical Test	Normal Levels
FBS	
3-11years	53-119mg/dL
12years+adult	<100mg/dL
SerumTotal Bilirubin	0-1.4mg/dL
SerumDirect Bilirubin	0-0.4mg/dL
SerumTotal Protein	6-8.3gm/dL
Serum Albumin	3.8-5.4gm/dL
Serum ALP	
7-9years (male)	86-315U/L
7-9years (female)	69-325U/L
10-12years (male)	42-362U/L
10-12years (female)	51-332U/L
SGPT (serum ALT)	0-50U/L
SGOT (serum AST)	0-60IU/L

FBS: fasting blood sugar; ALP: alkaline phosphatase; SGPT: serum glutamic pyruvic transaminase test; ALT: alanine aminotransferase; SGOT: serum glutamic oxaloacetic transaminase test; AST: aspartate aminotransferase; mg/dL: milligram per deciliter; gm/dL:gram per deciliter; U/L: unit per liter; IU/L: international unit per liter

Iraq during the period from October 2015 to December 2016. Their ages ranged from five to twelve years old. All were diagnosed and were under treatment in the hospital. All were subjected to multiple drug chemotherapy included γ-tocopherol (γTMT), methotrexate (MTX), vincristine (VCR), and 6-mercaptopurine (6-MP).

2.2 Blood Sampling

An overnight fasting venous blood samples were obtained from all eighteen under treatment children. Fasting blood sugar, serum total bilirubin, serum direct bilirubin, serum total protein, serum albumin, serum alkaline phosphatase, serum alanine aminotransferase, and serum aspartate aminotransferase were measured using autoanalyser device (Automated Mindray Ps200).

2.3 Statistical Analysis

Statistical analysis was done using SAS (Statistical Analysis System-version 9.0)[18].

3. RESULTS

Of eighteen, two cases (11.11%) showed low levels of serum glucose, serum total protein, serum albumin, serum alkaline phosphatase, normal levels of serum total bilirubin, serum alanine aminotransferase, and high levels of serum direct bilirubin, and serum aspartate aminotransferase. Two cases (11.11%) exhibited low levels of serum albumin, normal levels of serum glucose, serum total bilirubin, serum direct bilirubin, serum total protein, serum alkaline phosphatase, serum alanine aminotransferase, and high levels of serum aspartate aminotransferase. Two cases (11.11%) revealed normal levels of serum glucose, serum total bilirubin, serum direct bilirubin, serum total protein, serum albumin, serum alkaline phosphatase, and high levels of serum alanine aminotranferase, and serum aspartate aminotransferase. Two cases (11.11%) demonstrated low levels of serum total protein, serum albumin, normal levels of serum glucose, serum total bilirubin, serum direct bilirubin, serum alkaline phosphatase, and high levels of serum alanine aminotransferase, and serum aspartate aminotransferase. Two cases (11.11%) exhibited low levels of alkaline phosphatase, and normal levels of serum glucose, serum total bilirubin, serum direct bilirubin, serum total protein, serum albumin, serum alanine aminotransferase, and serum aspartate aminotransferase. Four cases (22.22%) revealed normal levels of serum glucose, serum total bilirubin, serum direct bilirubin, serum total protein, serum albumin, serum alkaline phosphatase, serum alanine aminotransferase, and serum aspartate aminotransferase. Two cases (11.11%) showed normal levels of serum glucose, serum total bilirubin, serum direct bilirubin, serum total protein, serum albumin, serum alkaline phosphatase, serum alanine aminotransferase, and high levels of serum aspartate aminotransferase. Finally, two cases (11.11%) exhibited low levels of serum total protein, serum albumin, normal levels of serum glucose, serum total bilirubin, serum direct bilirubin, serum alkaline phosphatase, serum aspartate aminotransferase, and high levels of serum alanine aminotransferase.

Table 2. Serum biochemical mean levels for pediatric patients enrolled in this study

Bibochemicl Levels / Biochemical Tests	No. of Cases & (%)	Low Levels (Mean±SE)	No. of Cases & (%)	Normal Levels (Mean±SE)	No. of Cases & (%)	High Levels (Mean±SE)
FBS	2 (11.11%)	22±1.00	16 (88.89%)	81.72±3.29	-	-
Serum Total Bilirubin	-	-	18 (100%)	0.36±0.08	-	-
Serum Direct Bilirubin	-	-	16 (88.89%)	0.01±0.01	2 (11.11%)	0.50±0.00
Serum Total Protein	6 (33.33%)	3.83±0.85	12 (66.67%)	6.71±0.13	-	-
Serum Albumin	8 (44.44%)	2.47±0.41	10 (55.56%)	3.94±0.05	-	-
Serum Alkaline Phosphatase	4 (22.22%)	20.50±11.83	14 (77.78%)	157±15.55	-	-
Serum ALT	-	-	12 (66.67%)	17.50±2.67	6 (33.33%)	136.66±37.74
Serum AST	-	-	8 (44.44%)	38.50±8.54	10 (55.56%)	238.60±39.15

No.: number; (%): percentage; Mean±SE: Mean±Standard Error; FBS: fasting blood sugar; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Of eighteen pediatric patients with acute lymphoblastic leukemia (ALL), twelve (66.66%) showed signs of liver disease. Of these twelve pediatric patients with liver disease, six (50%) experienced malnutrition, and of these six cases with liver disease and malnutrition, two (33.33%) suffered from hypoglycemia.

4. DISCUSSION

Leukemia infiltration of the liver is common at diagnosis of acute lymphoblastic leukemia (ALL). At the beginning of the malignant disease, it has been found a growth of the serum transaminases, a common affectation of the hepatic function, revealed by the serum transaminases modifications, which can be illustrated by the leukemic infiltration of the liver in the acute leukemia [19]. Abnormal serum alkaline phosphatase (ALP) concentrations are sign of liver infiltration. Determining serum albumin levels is frequently regarded as test of liver function. This is majorly because hepatic synthesis of albumin tends to decrease in end-stage liver disease. Albumin is produced by hepatocytes. Serum albumin may be considered interesting tool alone in clinical scores, for evaluating liver function [20]. A change in serum albumin concentration can be linked with a decrease in liver functioning mass, although it is not specific for liver disease. Around 1 to 2% of children with acute lymphoblastic leukemia (ALL) die before attaining remission, and an additional 1 to 2% die from toxic effects during remission. A person's risk of toxic effects is affected by host genetic factors that influence drug metabolism and activity. Thus, a considerable goal is the tailoring of drug exposure according to the estimated risk of both relapse and specific toxic effects . The folate analog methotrexate (MTX) and the thio-substituted purine analog 6-mercaptopurine (6MP) became pioneering anticancer drugs more than half a century ago, methotrexate (MTX) and 6-mercaptopurine (6MP) can induce remission in childhood leukemia [21]. Methotrexate (MTX) is a key therapy in the curative regimen of children with acute lymphoblastic leukemia (ALL). Methotrexate (MTX) is a potent hepatotoxic agent that causes injury of the liver correlated with impaired liver functions. The underlying mechanism of methotrexate (MTX) hepatotoxicity: methotrexate (MTX) results in oxidative stress in liver tissue as it is metabolized and stored in hepatocytes in a polyglutamates form which delays the clearance of methotrexate (MTX) offering a depot that extends the duration of exposure to the drug. 6-mercaptopurine (6MP) and methotrexate (MTX) are hepatotoxic and 2-fold increases or more of serum aminotransferases are frequent [22]. Hypoglycemic episodes during fasting have been associated with high concentrations of methylated 6-mercaptopurine (6MP) metabolites. A

moderate elevation in bilirubin during chemotherapy treatment is common, but the risk of serious and/or permanent liver damage looks low. Accordingly, most studies do not recommend dose reductions in case of high aminotransferase levels unless accompanied by biochemical proof of severe hepatic dysfunction, that is, bilirubin three times above the upper normal limit. Although tests that measure the concentrations of serum liver enzymes are commonly considered as liver function tests, they usually reflect hepatocyte integrity or cholestasis rather than liver function. Patients with toxic liver injury reach the highest aminotransferase levels. Aspartate aminotransferase (AST) levels usually peak before those of alanine aminotransferase (ALT) as a result of the enzyme's peculiar intra-lobular distribution [23]. In toxic liver injury, drug-induced liver injury is frequently associated with mild aminotransferase abnormality (<5 times the upper limit). Patients with high bilirubin serum levels must be closely monitored for the risk of hepatic failure. Methotrexate (MTX) hepatic and renal toxicity can result in discontinuation or reduction of chemotherapy doses which may affect the overall prognosis. Methotrexate (MTX) use is deemed of primary importance in the treatment of acute lymphoblastic leukemia (ALL), even if it is limited by its toxicity. Significantly, patients who continued therapy despite increase in aminotransferase had a lower relapse rates than patients with therapy interruptions due to hepatotoxicity. A child who is cured of acute lymphoblastic leukemia (ALL) is estimated to have 60 to 80 years remaining life. Unfortunately, many acute lymphoblastic leukemia (ALL) survivors do have chronic toxic effects[24].

Malnutrition represents the main problem in children experiencing from cancer. Its incidence differs according to the nature of the malignant disease, size, location, and the phase of the disease. Malnutrition represents an unfavorable prognosis element with children suffering from malignancy, it compromises the response to chemotherapy effects, the muscular function, reduces the survival rate, and elevates the incidence of infections [25]. Based on the biochemical parameters, the prevalence of malnutrition was higher among acute lymphoblastic leukemia children, so that 35.78% of the children showed hypoproteinemia at the beginning of the acute lymphoblastic leukemia, a percent which does not enhance, as a result a higher percent of malnutrition children remained. [26] explained in a prospective study on a group of 22 children with acute lymphoblastic leukemia (ALL) how hypoproteinemy affected the evolution of the disease and the response to the therapy in a negative way. Acute lymphoblastic leukemia pediatric patients suffer from liver infiltration due to malignancy and show hepatotoxicity due to the hepatotoxic nature of the chemotherapeutical agents used in leukemic treatments. Pediatric patients with liver diseases are prone to malnutrition. This is attributed to that pediatric patients have higher nutritional requirements and needs for growth and development than adults [27].

5. CONCLUSIONS

Malignancy of acute lymphoblastic leukemia (ALL) and hepatotoxicity because of chemotherapy treatment notably negatively affected the levels of the biochemical markers included in this study. Acute lymphoblastic leukemia disease and chemotherapy hepatotoxicity adversely affected liver function and nutritional status of pediatric patients enrolled in this study.

ETHICAL APPROVAL AND CONSENT

As per international standard or university standard written ethical approval has been collected and preserved by the author(s). Informed consent was obtained from children or their parents.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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