SERUM HEPCIDIN LEVEL AND DISEASE COURSE OF ACUTE LEUKEMIA IN CHILDREN

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ABSTRACT

Acute leukemia (AL) is a heterogeneous group of hematopoietic neoplasms and it is the most common childhood malignancy. Many patients with AL develop severe anemia that requires multiple blood transfusions. Hepcidin expression may play a role in anemia which is often seen in these patients. The aim of this study is to evaluate the role of hepcidin in acute lymphoblastic leukemia in children in Egypt. 60 patients with acute lymphoblastic leukemia (ALL) and 20 age and gender matched healthy children, taken as control group, were included in the study. Complete blood count (CBC), Serum ALT and serum AST were measured by colorimetric methods. Serum hepcidin and ferritin were measured by ELISA. The study showed a significant difference between newly diagnosed ALL cases and other groups regarding all CBC parameters. There was a significant difference in serum levels of hepcidin and ferritin between studied groups. A significant negative correlation was found between serum level of hepcidin and ferritin and each of hemoglobin level and reticulocytic count %, while significant positive correlation was found between hepcidin and ferritin serum levels. From this study, it could be concluded that serum hepcidin level is elevated in ALL children patients at time of diagnosis and correlates with the disease extent. Hepcidin may be one of the serum markers that accounting for anemia associated with ALL in children.

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INTRODUCTION

Acute leukemia (AL) is a heterogeneous group of hematopoietic neoplasms characterized by genetic abnormalities in a hematopoietic white cell give rise to an unregulated clonal proliferation of cells **(Mehdi et al., 2015 and Corazza et al., 1998)**. It is the most common form of cancer in children and it comprises 30% of all childhood malignancies, with acute lymphoblastic leukemia (ALL) being five times more common than acute myeloid leukemia **(Jemal et al., 2008)**. In Egypt, according to the National Center Registry (NCR) in 2002, acute leukemia constituting 36.7% of all cases of childhood cancer diagnosed annually, and acute leukemia is reported to be the first ranked in pediatric cancer **(Gadalla, 1996)**.

Ages range of 2- 5 years **(Margolin et al., 2006)**, male gender **(EL Attar et al., 2006)**, white race about 3-fold higher risk in white children compared to black children **(Smith et al., 2010)**, genetic syndromes such as Down syndromes, Neurofibromatosis, Bloom syndrome, Ataxia telangiectasia, and Klinefelter syndrome **(Whitlock, 2006)**, are reported to be risk factors of AL, also incidence of leukemia in twins is 4 times greater than that of the general population **(Lanzkowsky, 2011)**.

The human hepcidin gene contains three exons that encode an 84–amino acid preprohepcidin. Human hepcidin is a 25–amino acid peptide contains four disulfide bonds **(Hunter et al., 2002)**. The hepatocytes are the main cellular source of hepcidin but studies also detected hepcidin synthesis in bacteria-activated neutrophils and macrophages at a lower level than in hepatocytes **(Ganz, 2006)**.

Hepcidin acts by modulating cellular iron export through ferroportin to plasma and extracellular fluid **(Nemeth et al., 2004)**. When iron stores are adequate or high, the liver produces hepcidin, which circulates to the small intestine. There, hepcidin causes ferro-portin to be internalized, thus blocking the pathway for the transfer of iron from enterocytes to plasma and from macrophages. When iron stores are low, hepcidin production is suppressed **(Mark, 2008 and Ashby et al., 2009)**.

Anaemia is a constant feature in AL and mainly results from suppression of normal erythropoiesis in the bone marrow. Hepcidin may play a role in anaemia which is often seen in these patients **(Maes**

et al., <u>2010</u>). Few studies included hepcidin in leukemia so we aimed in this study to evaluate the role of hepcidin in acute lymphoblastic leukemia in children in Egypt and if it had a prognostic value in detecting remission.

MATERIAL AND METHODS

This study was carried out at Medical Biochemistry and Pediatric Departments, Faculty of Medicine, Menoufia University, in the period from March 2013 to April 2015. 60 ALL patients and 20 normal healthy children were enrolled in the study and were classified into four groups: group I included 20 newly diagnosed ALL patients (presence of more than 25% lymphoblast on bone marrow aspiration confirmed by immunophenotyping). Group II included 20 ALL cases after complete remission (normal values for absolute neutrophil count (>1000 /µl), platelet count (>100.000 /µl) and independent from red cell transfusion, bone marrow aspiration revealing normal maturation of all cellular components (i.e. erythrocytic, granulocytic and megakaryocytic series) and less than 5% blast cells, without leukemic phenotype. Group III included 20 maintenance children of ALL (maintenance phase, two or three years of treatment, from initial time of diagnosis, aims at a further stabilization of remission by suppressing the re-emergence of a drug-resistant clone) **(Crist et al., 1990 and Cheng et al., 2012)**. Group IV included 20 age and gender matched healthy children taken as control group.

Exclusion criteria of all groups were, patients with anaemia attributable to factors other than leukemia such as (haemolytic anemia and active inflammatory or infectious diseases, confirmed by C-reactive protein and blood culture,) or with serum creatinine > 0.7 mg/dl or serum total bilirubin > 1mg/dl or with acute myelogenous leukemia. None of these patients were receiving iron, recombinant human erythropoietin, chemotherapies and or blood transfusions prior to the start of our study. Fully informed written consent was obtained from the legal guardians of the studied children. The ethical committee of medical research of Faculty of Medicine, Menoufia University had approved the study.

All subjects were submitted to the following: full history taking, general and local clinical examination. Bone marrow aspiration was done for ALL patients.

Methods:

Five ml of venous blood was collected from all subjects, 2 ml into EDTA containing tubes, for CBC by coulter counter model Beckman 750 Int, U.S.A., and 3 ml was collected in plain vacutainer tube and was left to clot for 30 minutes at room temperature, then, centrifuged for 10 minutes at 3000 rpm and the serum obtained was stored at -20°C until the time of assay. Serum hepcidin was determined by enzyme linked immunosorbent assay method (ELISA), using EIAab® Human Hepcidin prohormone ELISA kit, China. Serum ferritin was determined by ELISA, using Monobind Inc, Human Ferritin ELISA kit, USA. Serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) were determined by kinetic UV optimized method IFCC (International fedration of clinical chemistry) (LTEC Kit, England).

Statistical analysis:

The data collected were tabulated and analyzed by SPSS (SPSS Inc., Chicago, IL, USA) statistical package version 20 on IBM compatible computer. Continuous parametric variables were presented as means±SD while for categorical variables numbers (%) were used. Chi-square test was used for qualitative variables. Quantitative data were analyzed by applying Anova test (for comparison between three groups of normally distributed variables) and Kruskal-Wallis Test (for comparison between three groups of not normally distributed variables). Pearson correlation was used to measure the association between two quantitative parametric variables, and Spearman correlation coefficient was applied for non-parametric data. Two-sided P-value of < 0.05 was considered statistically significant.

RESULTS

No statistically significant difference was found among the studied groups regarding age and gender (table 1). 35%, 75%, 45% and 100% of group I had lymphadenopathy, hepatosplenomegaly, bleeding and pallor, respectively. In group II and III there is no lymphadenopathy, hepatosplenomegaly or bleeding whereas pallor is present in 35% and in 30 % of patients of group II and III, respectively (data not shown). A significant difference was found between group I and other groups regarding all CBC parameters. Group I had significantly increased values of white blood cells (WBCs) while decreased values of

hemoglobin (Hb), platelet count, red blood cells (RBCs) count and reticulocytic count, compared to other patient and control groups. There is no significant difference between group II and III regarding all CBC parameters except WBCs count, whereas on comparing groups II and III with controls, significant difference was observed regarding Hb and platelet count. There was a significantly increased serum ALT level in group I compared to control, while there was no significant difference between other patient groups and control. Serum AST level was significantly increased in all patient groups compared to control. There was a significant difference in serum levels of hepcidin and ferritin between studied groups (table 2). A significant negative correlation was found between serum level of hepcidin and each of hemoglobin level and reticulocytic count %, while significant positive correlation was found between serum levels of hepcidin and ferritin among group I, however, no significant correlation was found between serum hepcidin level and laboratory parameters among group II and III (table 3). A significant negative correlation was found between serum level of ferritin and each of hemoglobin level, RBCs and reticulocytic count % among group I, however, no significant correlation was found between serum ferittin level and all laboratory parameters among group II and III (table 4).

Table (1): Demographic characteristics of the studied groups.

	Studied groups				Test	P value
	Patients			Control		
	Group I (n=20)	Group II (n=20)	Group III (n=20)	Group IV (n=20)		
Age (years) Mean±SD Range	2.80 ±1.12 1.00 – 6.00	2.85±1.06 1.50 – 6.00	2.80 ± 0.97 2.00 – 6.00	3.17 ± 0.63 2.00 – 4.50	**K**=5.59	0.13
Gender :	No %	No %	No %	No %	$\chi2$ =0.22	0.97
Male	13 65.0	13 65.0	14 70.0	14 70.0		
Female	7 35.0	7 35.0	6 30.0	6 30.0		

Group I: Newly diagnosed ALL patients, Group II: ALL patients at complete remission, Group III: ALL patients in maintenance, Group IV: Healthy controls. K: Kruskal Wallis test, $\chi2$: Chi square test. P-value of < 0.05 was considered statistically significant.

Table (2): Statistical comparison between the studied groups regarding laboratory parameters

	Patient groups			Control	P value	Post Hoc test	
	Group I (n=20) Mean±SD	Group II (n=20) Mean±SD	Group III (n=20) Mean±SD	Group IV (n=20) Mean±SD			
Hb (gm/dl)	6.1±2.1	10.8±1.1	11.0±0.9	12.6±0.4	<0.001*	P1<0.001 P2<0.001 P3<0.001	P4=0.55 P5<0.01 P6<0.01
Platelets count (x10³/ml)	61.2± 47.1	214.4±82.6	250.3±60.7	307.50±33.06	<0.001#	P1<0.001 P2<0.001 P3<0.001	P4= 0.55 P5=0.001 P6=0.005
WBCs count (x10³/ml)	33.5±23.4	2.8±1.4	4.4±0.5	5.4±0.9	<0.001#	P1<0.001 P2<0.001 P3<0.001	P4<0.001 P5= 0.49 P6= 0.80
RBCs count (x 10⁶ /ml)	2.6±0.9	3.8±0.7	6.2±8.4	4.9±0.3	<0.001#	P1<0.001 P2= 0.01 P3<0.001	P4= 0.09 P5= 0.45 P6= 0.98
Reticulocytic count (%)	1.4 ± 0.7	2.08 ± 0.2	2.05 ± 0.2	2.11 ± 0.1	<0.001#	P1=0.002 P2=0.003 P3=0.001	P4= 0.77 P5= 0.80 P6= 0.58
Serum ALT (IU/L)	13.9± 3.2	13.2± 1.9	13.1± 1.9	11.9± 0.9	0.04*	P1= 0.30 P2= 0.24 P3=0.006	P4= 0.88 P5= 0.07 P6= 0.09
Serum AST (IU/L)	29.8±6.1	28.2±3.5	28.6±4.1	24.1±3.3	0.001*	P1= 0.25 P2= 0.41 P3<0.001	P4= 0.74 P5=0.005 P6=0.002
Serum ferritin (ng/ml)	1265.3±252.9	793.5 ±206.5	604.3 ±184.7	166.6 ±44.3	<0.001*	P1 0.001 P2<0.001 P3<0.001	P4=0.002 P5<0.001 P6<0.001
Serum hepcidin (ng/ml)	387.6 ± 60.9	221.5 ± 36.4	181.9 ± 22.7	69.8 ± 9.7	<0.001*	P1<0.001 P2<0.001 P3<0.001	P4=0.001 P5<0.001 P6<0.001

Group I: Newly diagnosed ALL patients, Group II: ALL patients at complete remission, Group III: ALL patients in maintenance, Group IV: Healthy controls.*F: Anova test, #K: Kruskal Wallis test. P1: G I Vs. G II, P2: G I Vs. G III, P3: G I Vs. G IV, P4: G II Vs. G III, P5: G II Vs. G IV, P6: G III Vs. G IV. P-value of < 0.05 was considered statistically significant.

Table (3): Correlation between serum hepcidin and laboratory parameters among patient groups

	Serum hepicidin					
	Group I		Group II		Group III	
	r	P value	r	P value	r	P value
Hb (gm/dl)	- 0.54	**0.01**	0.06	0.82	- 0.19	0.41
Platelets (×10³/ml)	- 0.11	0.67	0.19	0.48	0.009	0.96
WBCs (×10³/ml)	0.66	0.11	0.25	0.34	0.40	0.07
RBCs (x 10^6 /ml)	- 0.48	0.06	0.31	0.24	- 0.34	0.14
Retics %	- 0.62	**0.003**	- 0.11	0.67	- 0.005	0.98
ALT (IU/L)	- 0.30	0.25	-0.22	0.40	0.07	0.74
AST (IU/L)	- 0.53	0.19	- 0.09	0.74	- 0.21	0.36
Serum ferritin (ng/dl)	0.81	**<0.001**	0.04	0.86	- 0.29	0.20

Group I: Newly diagnosed ALL patients, Group II: ALL patients at complete remission, Group III: ALL patients in maintenance, Group IV: Healthy controls. r: Pearson correlation or Spearman correlation. P-value of < 0.05 was considered statistically significant.

Table (4): Correlation between serum ferritin and laboratory parameters among patient groups

	Serum ferritin					
	Group I		Group II		Group III	
	r	P value	r	P value	r	P value
Hb (gm/dl)	- 0.46	**0.04**	0.50	0.18	0.04	0.86
Platelets (×10³/ml)	0.07	0.79	- 0.23	0.37	- 0.18	0.44
WBCs (×10³/ml)	0.21	0.42	- 0.06	0.82	- 0.31	0.17
RBCs (x 10^6 /ml)	- 0.59	**0.02**	- 0.04	0.86	0.11	0.62
Retics %	- 0.52	**0.02**	- 0.02	0.92	- 0.39	0.08
ALT (IU/L)	- 0.33	0.21	0.22	0.40	- 0.11	0.62
AST (IU/L)	- 0.27	0.31	- 0.01	0.96	- 0.02	0.91

Group I: Newly diagnosed ALL patients, Group II: ALL patients at complete remission, Group III: ALL patients in maintenance, Group IV: Healthy controls. r: Pearson correlation or Spearman correlation. P-value of < 0.05 was considered statistically significant.

DISCUSSION

Acute lymphoblastic leukemia (ALL) constitutes about 75% of pediatric acute leukemias. Evidence from studies in iron deficient cancer patients with anemia highlights the importance of monitoring blood iron parameters **(Schrijvers et al., 2010)**. The hepcidin–ferroportin axis plays a critical role in the metabolism of iron, and may thus indirectly influence the development and prognosis of cancer. Both hepcidin and ferroportin work together to regulate the uptake and distribution of iron around the body **(Wu et al., 2014)**. The aim of this work was to evaluate the role of hepcidin in acute lymphoblastic leukemia in children.

The current study showed that age and gender were matched between patients groups (new cases of ALL, complete remission and maintenance groups) and control group. The study also showed predimonance of male gender 65% and 70% in groups I and II, respectively, than female gender 35% and 30 % in groups III and IV, respectively, of ALL cases, these results agree with previous results **(Khalifa et al., 1999; Pearce and Parker, 2001; Hasanbegović, 2006; Martin et al., 2007; Svendsen et al., 2007 and Seiter et al., 2014)**.

In Egypt a higher incidence of ALL was observed in the age group (0 -10 years) and regarding sex incidence, the male to female ratio was 1.7:1 which comes in agreement with our results but they were in disagreement with us regarding the mean age at presentation as they reported it by 5.55±3.5 which is more than our mean (2.8 ± 1.12) **(Khalifa et al., 1999)**. Another study in Egypt in national cancer institute (NCI) in (2005), reported that the number of diagnosed cases with ALL was 125 (60.4%) males and 82 (39.4%) females **(EL Attar et al., 2006)**.

There was a great risk in boys compared to girls reported by cancer registries in developed countries, Asia and Africa. This is unlikely to reflect biological differences in susceptibility by sex, rather it reflects uneven access for boys and girls to centers specialized in cancer treatment where sick girls are less likely than boys to reach specialized care **(Pearce and Parker, 2001)**.

The present study reported that Group I patients had statistically highly significant clinical criteria (Lymphadenopathy,

hepatosplenomegaly, bleeding and pallor) than complete remission, maintenance and control groups. These results agree with those reported by previous results (**Hasanbegović, 2006 and Khalid et al., 2010**). Clinical criteria of ALL result from the lack of normal and healthy blood cells because they are crowded out by malignant and immature leukocytes, therefore, people with ALL experience symptoms from malfunctioning of their erythrocytes, leukocytes, and platelets (**Seiter et al., 2014**).

In the current study, group I patients had significantly increased values of WBCs while decreased values of Hb, platelet count, RBCs count and reticulocytic count compared to both group II and controls. These results agree with those reported by other results (**Hasanbegović, 2006 and Khalid et al., 2010**). The leukocytic count was statistically decreased after chemotherapy in complete remission, these results agree with **Eyrich et al., (2009)** whom reported that leukocytes count and lymphoblast level were statistically significantly decreased in ALL patients after chemotherapy compared to before chemotherapy. In contrast to our results, **El- Sabagh et al., (2011) and Zou et al., (2010)** reported that hemoglobin level was significantly decreased in ALL patients after chemotherapy compared to before chemotherapy.

Sheikh et al., reported that increased WBC count is the most important parameter that suspects the leukemia. WBC count >30,000/mm³ is an indication of bone marrow abnormality (**Eyrich et al., 2009**).

Anemia is a common manifestation in patients with leukemia, and this can be monitored by periodically measuring hemoglobin status, hemoglobin levels less than 11g/dL are typically seen with leukemia (**Quirt et al., 2001**).

In this study platelets count in new cases was statistically significantly decreased at time of diagnosis (as one of the presentation of ALL) in comparison with other groups. Similar results are also reported (**Peter, 2002; Eyrich et al., 2009 and El-Sabagh et al., 2011**). Decreased platelets count was explained by (Nasri and Baradaran, 2006) due to abnormalities of stimulus in platelet production and platelet-endothelial interactions. Reduced platelet aggregation and adhesiveness leads to defective blood clotting, which ultimately results in increased bleeding (**Nasri and Baradaran, 2006**).

The current study showed that serum levels of ALT and AST were significantly increased in new cases than control group while they were not statistically significant different between the three patient groups. Similar results have been reported by Mantovani et al., **(Mantovani et al., 2004)**. These high levels of liver enzymes reflect the extent of liver damage i.e. necrosis of erythrocytes or hepatocytes **(Sheikh et al., 2006)**.

The present study showed highly significant increase in serum hepcidin in new cases group compared with other patient groups and controls. Also, complete remission group had significantly increased serum hepcidin level when compared with maintenance and control groups **(Piperno, 1998; Arvedson et al., 2008; Nemeth, 2008 and Maccio et al., 2014)**. High erythropoietic activity generates a signal that can override hepcidin regulation by iron, when erythropoiesis is inhibited in untreated patients with ALL, hepcidin is regulated mainly by increased extra cellular iron storage. However, when erythropoiesis recovered during remission period, hepcidin decreased significantly even though iron overload is still existed **(Nemeth, 2008)**, similar results were reported by **Cheng et al, (2012)**.

In the present study serum ferritin was significantly increased in new cases than other patient groups and control group and was significantly increased in complete remission group than control group. These results are supported with those reported by other studies **(Piperno, 1998 and Porter, 2001)**.

Porter, (2001) found that, anemia is a constant feature in AL and mainly results from suppression of normal erythropoiesis in the bone marrow by infiltrating blasts or drug-induced bone marrow depression in patients receiving chemotherapies. Many patients with AL develop severe anaemia that requires multiple blood transfusions. As every unit of RBC supplies the body with 200–250 mg of iron while daily iron loss from the body is limited to only 1–2 mg, dependency on 2 transfusions TU of RBC∕ month results in an increase in body iron stores by approximately 5 g and increase in serum ferritin by > 1000 g∕L per year.

In anemia owing to ineffective erythropoiesis, the erythroid regulator also increases iron absorption, but in the absence of iron losses, the accumulation of iron eventually results in iron overload and increase in serum ferritin **(Nemeth, 2008)**.

A significant positive correlation was found, in this study, between serum levels of hepcidin and ferritin in group I of patients and negative correlation between serum hepcidin and hemoglobin values and reticulocytic count in the same group, these results are supported with those reported by (**Zipperer et al., 2013 and Mei et al., 2014**). Also, in the current study there was a significant negative correlation between serum ferritin and hemoglobin values, reticulocytic count and RBCs count in group I of patients, these results agree with results reported by **Cermák et al (1994)**.

Conclusion:

Serum hepcidin may be useful as a marker of disease extent, as its level is elevated in ALL children patients at time of diagnosis and relatively decrease in complete remission. Hepcidin may be one of the mechanisms accounting for the anemia related to the disease, so, the use of hepcidin antagonists in conjugation with erythropoiesis stimulating agents (ESAs) in management of the associated chronic anemia may be benefit especially in patients whom develop resistance or adverse effects of ESAs.

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الملخص العربى

نسبه الهيبسيدين فى مصل الدم ومسار مرض سرطان الدم الحاد فى الاطفال

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سرطان الدم الحاد هي مجموعة غير متجانسة من الأورام المكونة للدم تعمل على إنتاج كميات كبيرة من خلايا الدم البيضاء المسرطنه والتي لا يمكنها القيام بوظيفتها الطبيعية وتحد من قابلية الجسم على إنتاج خلايا الدم الحمراء والأجسام الصفيحية وهو اكثر الاورام انتشارا فى الاطفال. الهيبسيدين هو هرمون ببتيدي ينتجه الكبد يتكون من ٢٥ حمض امينى ويعتبر المنظم الرئيسي لتوازن الحديد في جسم الإنسان حيث يعمل الهيبسيدين على التثبيط المباشر للفيروبورتين وهو بروتين ينقل الحديد خارج الخلايا المخزنة له.

الغرض من البحث: تقييم نسبه الهيبسيدين فى مصل الدم للاطفال المصابين بسرطان الدم الليمفاوى الحاد.

المرضى وطرق البحث: أجريت هذه الدراسة على ثمانين طفلا ، ستون طفلا مصابين بسرطان الدم الليمفاوى الحاد (وتم تقسيمهم الى ٣ مجموعات المجموعة الأولى: تتضمن عشرين طفلا وقت تشخيص الحاله، المجموعة الثانية تتضمن عشرين طفلا بعد تقلص كلى للمرض، المجموعة الثالثه وتتضمن عشرين طفلا اثناء مرحلة المحافظة) أما المجموعة الرابعة فتضمنت عشرين من الاطفال الأصحاء كمجموعة ضابطة. وقد تم أخذ التاريخ المرضى وفحص إكلينيكى شامل، تعداد كامل الدم ، قياس انزيمات الكبد، وقياس نسبة كل من الهيبسيدين والفريتين فى مصل الدم لكل من المرضى والأصحاء.

النتائج: أظهرت نتائج هذه الدراسة وجود زيادة ذات دلالة إحصائية فى نسبة الهيبسيدين فى مرضى سرطان الدم الليمفاكى الحاد مقارنة بنسبته بعد تقلص المرض وكذلك بالمجموعة الضابطة. كشفت الدراسة أيضا وجود توافق ايجابى ذو دلالة إحصائية بين مستوى الهيبسيدين والفيريتين بينما يوجد توافق سلبى بين الهيبسيدين ونسبه الهيموجلوبين كما أنه لا يوجد توافق بين مستوى الهيبسيدين فى مرضى سرطان الدم الليمفاوى الحاد مع نسبه كرات الدم البيضاء الصفائح ووظائف الكبد.

الاستنتاج: يمكن الاستنتاج بأن مستوى الهيبسيدين فى مصل الدم يرتفع فى الأطفال المصابين بسرطان الدم الليمفاوى الحاد في وقت التشخيص ويرتبط بمراحل المرض. هيبسيدين قد تكون واحدة من علامات المصل الذي يمثل فقر الدم المرتبط بسرطان الدم الحاد في الأطفال والذى من الممكن استخدامه فى علاج هؤلاء الأطفال.