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Evaluation of the Serum Levels of Thyroid Hormones in Newly Diagnosed Patients with Chronic Lymphocytic Leukemia

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ABSTRACT

Background: Chronic lymphocytic leukemia (CLL) is the most prevalent form of adult leukemia in Western societies, constituting 25% of all adult leukemias and 25% of non-Hodgkin lymphomas. The current work designed to evaluate the serum levels of thyroid hormones as an indicator of prognosis for newly diagnosed chronic lymphocytic leukemia.

Patients and Methods: This research employed a cross-sectional design and included fifty newly diagnosed patients. All patients were chosen from outpatient clinic and inpatients of Internal Medicine department, Al-Azhar University Hospitals (Damietta). All submitted to systematic clinical evaluation. Then, thyroid hormones were measured and correlated with the disease severity.

Results: There was significant correlation between Free T3, spleen size, white blood cells, absolute lymphocytic count, platelet count, C-reactive protein, and albumin. Although no substantial correlation was observed between free T3, age, hemoglobin and free-t4. Area under the curve was 0.57 for differentiation between mild and moderate conditions. Area under the curve was 0.81 for differentiate between mild and severe conditions (p=0.003).

Conclusions: Thyroid hormones in cases of CLL could be used as predictors of disease severity and prognosis.

Keywords: Thyroid hormones; Thyroxine; Thyroid Stimulating Hormone; Chronic Lymphocytic Leukemia.

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INTRODUCTION

Thyroid hormones (TH), specifically T3 and T4 play Adult chronic lymphocytic leukemia (CLL) is the most prevalent form of leukemia in the Western countries. It representing twenty-five percent of all adult leukemias and twenty-five percent of all non-Hodgkin lymphomas (NHL) [1,2].

There is an elevated incidence of CLL among patients who have been exposed to Agent Orange and have a family history of the disease [3].

At present, the accurate immunophenotype of lymphocytes base on peripheral blood or bone marrow is utilized to diagnose CLL. World Health Organization in 2016 developed the guidelines for the diagnosis and treatment of CLL. Certain criteria must be met. These include peripheral blood monoclonal B-lymphocytes at least five thousand lymphocytes/µl for a minimum of three months; flow cytometry demonstrating co-expression of CD5 and B-cell surface antigens CD19, CD20, and CD23; and sIg, CD20, CD79b, and kappa or lambda light chain restriction at low levels [4,5].

Situated in the neck, the thyroid gland is an endocrine organ in the shape of a butterfly. The prohormone thyroxine (T4) is the principal form of thyroid hormone secreted in response to thyroid stimulating hormone (TSH). 5′-deiodinase enzymes are necessary for tissues to convert this prohormone into its active form tri-iodothyronine (T3) [6-8].

The precursor elements of these thyroid hormones are tyrosine and iodine. The amino acid tyrosine & iodine are combined in the synthesis of these thyroid hormones. Various systemic organic and metabolic responses are elicited when they are introduced into the bloodstream. In addition to metabolic processes involving carbohydrates, lipids, and proteins, thyroid hormone regulates oxygen consumption and basal metabolic rate (BMR). It exerts basic effects on the nervous system and controls the rates of production and breakdown of numerous proteins [9,10].

T3 is formed in conjunction with thyroglobulin, a protein that is recognized as the prohormone to thyroxine. Thyroglobulin is equipped with iodine trapping mechanisms that result in the formation of precursors mono-iodotyrosine (MIT) & diiodotyrosine (DIT) [11,12].

Levels of thyroid hormones were studied in different conditions (e.g, chronic and critical illness, some tumors, liver and renal failures). However, it is not studied in CLL. Thus, the objective of this research endeavor was to assess the prognostic value of serum thyroid hormone levels in newly diagnosed patients with chronic lymphocytic leukemia who are at high risk.

PATIENTS AND METHODS

This research was a cross-sectional design and included fifty recently diagnosed patients as CLL according to diagnostic criteria. All patients were selected from the outpatient clinic and inpatient of Internal Medicine department of Al-Azhar University Hospital (Damietta).

Inclusion criteria:

Patients aged 40-80 years, of both genders, who were newly diagnosed as CLL. This based on the complete blood count (CBC), bone marrow and immunophenotyping.

Exclusion criteria:

Patients with history of diseases leading to affection of thyroid hormones (e.g., age less than 40 years, patients suffering from chronic diseases and patients with thyroid diseases).

Methods

All patients were evaluated by full history taking and clinical examination. In addition to the laboratory workup that included complete blood count (CBC) using an automated hematology analyzer, peripheral blood film, and tests for liver function (ALT, AST, serum albumin, and total bilirubin) by Roche Cobas c 311, Serum levels of TSH, T3 Free, T4 free by chemiluminescence, Immunophenotyping (CD5, CD10, CD13, CD19, CD20, and CD79b, Anti-FM7) by flowcytometry. Glassgow prognostic score. The patients were assessed in the following manner: those who had both hypoalbuminemia (<3.5g/dl) and an elevated CRP concentration (>1mg/dl) were awarded 2 points; those who had hypoalbuminemia or elevated CRP alone received 1 point; and those who were within the normal range were awarded no points.

Ethical Considerations

The subjects were selected and specimens were collected from them subsequent to a thorough explanation of the research's goals. Written consent was obtained from participants of their own free will, and the entire research was conducted in adherence to the guidelines set forth by the ethical committee of the Faculty of Medicine, Al-Azhar University.

Statistical analysis

The recorded data were summarized by the mean ± SD for quantitative data and relative frequencies and percentages for categorical data. The disease grades (mild, moderate, and severe) were compared by the one-way analysis of variance. The correlation between variables were calculated by Pearson's correlation coefficient. The predictive power of thyroid hormone (free T3) was measured by the receiver operation characteristics curve. The p value < 0.05 was considered significant.

RESULTS

The mean age of study populations was (66.7 ± 5.8) years, 78% were females while 22% were males (table 1). CD5 median (IR)*x 10^3 was 8.9 and ranged from 8.6 to 9.5. CD19 median (IR) x 10^3 was 3.6 and ranged from 2.1 to 4.2. 50. All of patients were negative CD79b and CD

FMC7 (Table 2).

Classifying patients on the basis of disease severity showed that, 12 were mild, 16 were moderate and 22 had severe disease. Comparing mild, moderate and severe cases showed that, no significant differences were recorded for hemoglobin concentrations, thyroid stimulating hormone and free T4. However, while blood cells, absolute lymphocytic count, increased in server than moderate and mild cases. On the other side platelet count and free T3 were significantly reduced in sever than mild and moderate cases (Table 3).

Searching the correlation between Free T3 and other variables revealed that, there was significant negative correlation between Free T3 from one side and each of spleen size, white blood cells, absolute lymphocytic count, CRP, TSH and Free T4. On the other side, the correlation was proportional with platelet count and albumin (Table 4).

Building the receiver operative characteristic (ROC) curve to check the diagnostic power of free T3 revealed that, T3 could differentiation between mild and severe cases (AUC = 0.81 and p = 0.003). However, it could not differentiate between mild and moderate cases (AUC= 0.57, p =0.133) (Table 5, figure 1).

Table (1): Demographic data of the studied cases

Demographic data	Results
Age (years): Mean ± SD	66.7 ± 5.8
Gender: No. (%) • **Female:** • **Male:**	 39 (78%) 11 (22%)

Table (2): Immunophenotyping (IPT) data of the studied cases

IPT data	Results
CD5 median (IR)*x 10^3	8.9 (8.6 – 9.5)
CD19 (IR)x 10^3	3.6 (2.1 – 4.2)
CD79b: Negative	50 (100%)
CD FMC7: Negative	50 (100%)

IR: Interquartile range

Table (3): Hematological data of the studied cases based on severity

Variables	Mild (n=12)	Moderate (n=16)	Severe (n=22)	P value
Hemoglobin (g/dl)	10.1±2.2	10.6±2.3	9.8±1.8	0.51
White blood cells (×10^9 /L)	49.8±21.0	56.5±15.5	105±22.4	<0.001
Absolute Lymphocytic count (×10^9 /L)	43.3±19.8	46.3±13.1	90.2±23.0	< 0.001
Platelet count (×10^3 /L)	94.5±33.4	85.2±22.9	56.3±14.6	< 0.001
TSH (miu/ml)	2.1±1.4	2.2±1.1	3.2±1.2	0.06
FT4 (ng/dl)	1.3±0.34	1.4±0.64	1.4±0.65	0.55
FT3 (pg/ml)	3.4±0.67	3.4±0.55	1.6±0.13	< 0.001

Table (4): Correlation of Free T3 with other parameters in studied cases

	Free T3	
Variables	***r***	**P value**
Age (years)	-0.035	**0.811**
spleen size	-0.640	**P < 0.001**
Hb (g/dL)	0.165	**0.253**
WBC (×109/L)	-0.700	**P < 0.001**
Absolute Lymphocytic count	-0.63	**P < 0.001**
Platelet count (×10^9/L)	0.548	**P < 0.001**
CRP (mg/ml)	-.0549	**P < 0.001**
Albumin (gm/dl)	0.707	**P < 0.001**
TSH (miu/ml)	-0.422	**0.002**
FT4 (ng/dl)	**-0.064**	**0.656**

Table (5): Free T3 in differentiation between grades of CLL

	AUC	Standard error	P	95% CI	
				Lower	Upper
Mild vs moderate	0.57	0.113	0.54	0.35	0.79
Mild vs severe	0.81	0.107	0.003	0.61	1.0

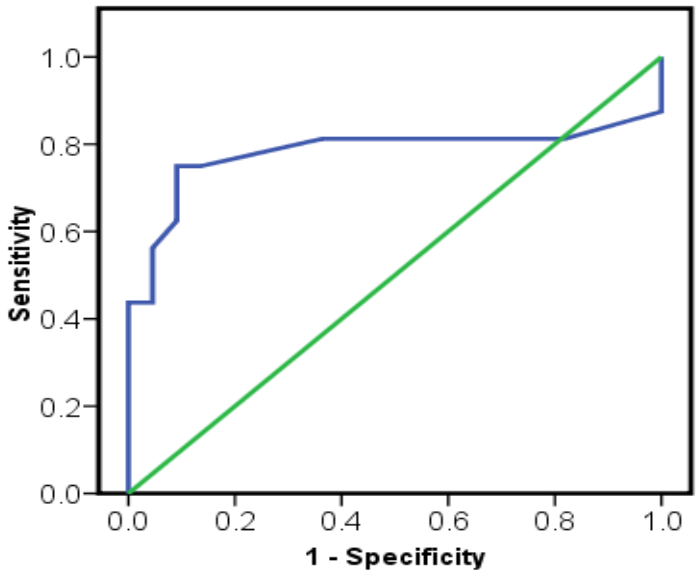

Figure (1): ROC and AUC for differentiate between mild and severe

DISCUSSION

The main results of the current work showed that, there was significant reduction of Free T3 in severe than moderate and mild cases. However, T4 and TSH showed non-significant differences. In addition, FT3 negatively correlated with spleen size, white blood cells, absolute lymphocytic count, CRP and TSH. It can differentiate mild than severe cases. But it could not differentiate mild than moderate cases.

Chronic lymphocytic leukemia (CLL) primarily affects the elderly population. Due to its frequent occurrence as a relatively dormant condition accompanied by extended survival periods for numerous patients, chronic lympho-blastic leukemia (CLL) is the most prevalent form of adult

leukemia in western nations [13].

Hematological data of studied cases showed that hemoglobin levels were 10.1±2.1 g/dl which indicated anemia in cases of CLL. This may be due to infiltration of the bone marrow by monoclonal cells of CLL. This confirms the data of 2018 International Workshop on CLL (iwCLL) treatment indications which stated that presence of anemia is a worsening sign in response to gradual marrow failure [14]. Also, Anemia may be due to auto-immune hemolytic anemia, as it was manifested in ten to fifteen percent of cases at the time of diagnosis in a previous study. AIHA exhibits considerable variability, ranging from completely compensatory to potentially fatal. It can be induced by complement activation or non-activation of autoantibodies targeting red blood cells (RBCs). Primary causes of AIHA include underlying conditions such as lymphoproliferative disease (20%), infections (20%), immunodeficiency, and malignancy. Idiopathic AIHA accounts for 50% of cases [15].

The results of the current work are comparable to those reported by **Docter *et al.*** [16] CLL is associated with low (T3) syndrome and in more severe cases also in tetraiodothyronine (T4) levels. But, not associated with a usual feedback increase in TSH.

The reduced levels of T3 may aggravate the clinical problems associated with prolonged critical illness such as CLL [17]. The reduced levels also denoting unfavorable outcome in other chronic conditions (e.g., sepsis, myo-cardial infarction (MI), heart failure, cerebrovascular accidents, liver cirrhosis, renal and respiratory failure [18-22].

In addition, reduced T3 is associated with malignancies. For example, **Bunevicius *et al.*** [23,24] reported lower T3 and it was correlated with poor prognosis and short survival in patients with glioma. **Yasar *et al.*** [25] and **Cengiz *et al.*** [26] also reported low T3 as an indicator of poor prognosis in patients with lung cancer, especially in non-small-cell lung cancer. **Gao *et al.*** [27] also reported low T3 in diffuse large B-cell lymphoma.

Furthermore, our results are comparable to those reported by **Gao *et al.*** [28] who reported low thyroid hormones, especially T3 as a predictor in patients with CLL. The pathophysiologic correlations between reduced T3 levels and malignancies are not fully understood. However, thyroid hormones measurement is a simple, readily available, with ease in their measurement. They could provide a good prognostic indicator for CLL in clinical practice. The same authors reported significant correlation between disease severity the T3 levels as in the current work. This correlation was also reported in other malignancies (e.g., brain tumors and lung cancer) [23-25].

Proinflammatory cytokines may play a role for the reduced release of TSH in cases with severe deficiency of T3, but with affection of other hormones of pituitary gland (e.g., adrenocorticotropic and growth hormones) [29].

In line with the current results, **Fan *et al.*** [22] reported a significant correlation between serum T3 from one side and hemoglobin concentrations, serum albumin and CRP indicated that, low T3 is associated with malnutrition, inflammation and anemia.

Finally**, Gao *et al.*** [28] suggested that, the potential pathogenetic mechanisms of reduced thyroid hormone in cancers could be partially explained by central hypothyroidism, changes in binding of hormone, modification of the thyroid hormone entry into tissue, alterations in the expression of iodothyronine deiodinases and thyroid hormone receptors. They added in chronic disease like CLL, the pathogenic mechanism is complex, multifactorial and bidirectional (e.g., inflammation, malnutrition and anemia). Current results confirm this hypothesis. **Singer *et al.*** [30] reported a role of cytokines as tumor necrosis factor -alpha in pathogenesis of T3 deficiency in CLL.

In conclusion, low thyroid hormones, mainly T3 could be used as an indicator and prognostic marker in patients with CLL. However, due to absent comparative (control group), single centre study with small number of patients (all constitute the limitations of the current work), the results must be validated in future studies before generalization.

Conflict of interest and financial disclosure: none

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