

Thyroid Stimulating Hormone in Patients with Macrocytic Anemia

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Abstract

Background Aims: The study aimed to examine the frequency of hypothyroidism among patients with macrocytic anemia and to compare this with the frequency of megaloblastic anemia.

Materials and Methods: Routinely transferred specimens for a complete blood count test were sent to the hematology lab in our institution and prospectively screened for high mean cell volume (MCV). A total of 100 cases with macrocytosis were examined for the levels of thyroid stimulating hormone (TSH), vitamin B12 and folate levels. Statistical analysis was performed to investigate a potential association between hypothyroidism and other variables.

Results: There were 52 women and 48 men. The range of age was 21–83, with a mean of 59 years. The mean MCV was 104.18 fL, while the mean hematocrit was 35.96%. Fifty-three (53%) patients had anemia. Eighteen (18%) patients had TSH level above the normal range qualifying for hypothyroidism. Among these, eight (44%) had low hematocrit and six (33%) a concomitant megaloblastic anemia. The presence of high TSH level did not show a statistically significant correlation with gender, age, vitamin B12, folate or hematocrit levels.

Conclusions: Hypothyroidism is commonly present in patients with macrocytosis. Its frequency is comparable with megaloblastic anemia, and both can occur simultaneously. Routine TSH level testing is recommended in patients with macrocytosis even if hematocrit level is normal or if the patient has megaloblastic anemia.

Keywords: Hypothyroidism, Anemia, Macrocytic, TSH, Megaloblastic

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Introduction

Anemia is a common disease that represents a major health problem, especially in developing countries, affecting the general health, quality of life and working efficiency of millions of people. According to the World Health Organization, anemia affects approximately two billion people globally [1]. There are many causes of anemia, most of which are nutritional. In addition, anemia frequently coexists with diseases that are

common in the population, such as obesity and hypothyroidism [2,3].

Hypothyroidism is another frequent medical condition with an estimated prevalence of 2–5% of the population [3]. Worldwide, dietary iodine deficiency is the main etiology of the disease, while Hashimoto's thyroiditis is the most common cause in iodine sufficient persons. With the exception of the very rare central (pituitary) cause of hypothyroidism, the diagnosis is

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made when thyroid-stimulating hormone (TSH) level is elevated in the blood. Treatment is essentially implemented by hormonal replacement with levothyroxine. If the disease remains undetected, overt hypothyroidism will have negative consequences for the mental and general health of individuals [3].

Anemia is a common finding in hypothyroid patients. Different forms of anemia can develop during the course of hypothyroidism [3]. Macrocytic anemia, defined by the presence of red blood cells (RBC) with a mean cell volume (MCV) above normal, can be seen in hypothyroidism. Megaloblastic anemia is very common and notoriously causes macrocytic anemia. Consequentially, it can mask coexisting hypothyroidism in routine clinical practice. In this study, the frequency of hypothyroidism among patients with high MCV and its relationship with megaloblastic anemia were investigated.

Materials and Methods

This is a prospective, cross sectional, pilot study where 100 cases were sequentially collected. The rationale of the study was to provide a general overview of the frequency of hypothyroidism among patients with macrocytosis, but not to investigate other causes thoroughly or determine the type of hypothyroidism. The study was approved by the Committee of Scientific Research and the Institutional Review Board.

Complete blood count (CBC) tests were performed using peripheral blood samples that were transferred to the hematology laboratory at Jordan University Hospital between March and June, 2020, using EDTA tubes at room temperature. The tests were routinely screened to identify cases with macrocytosis, defined by

MCV ≥ 100 fL (ADVIA 120 Hematology System, Siemens Healthineers, USA), representing the inclusion criterion for the study. For every case with macrocytosis, blood film was examined to confirm the presence of macrocytic red blood cells and exclude conditions that potentially raise MCV without the presence of macrocytosis, such as marked reticulocytosis and RBC agglutination.

Positive cases were segregated for further tests. Relevant data on gender, age, and hematocrit (Hct) were retrieved for the study group. Anemia was defined by Hct $< 36\%$ in women and $< 38\%$ in men. To investigate the possible association of age with macrocytosis, patients were segregated into the following age categories: < 20 , 20–39, 40–59, 60–80 and > 80 .

Samples of serum from patients with macrocytosis were transferred in plain tubes at room temperature for assessment of thyroid stimulating hormone (TSH), vitamin B12 and folate levels. The tests were performed using Chemiluminescence Microparticle Immunoassay (CMIA) technology according to the manufacturer's protocol. Control materials were routinely run with each test. The normal reference ranges were .4–4.0 $\mu\text{IU/mL}$ for TSH, 200–900 ng/mL for vitamin B12 and 2–20 ng/mL for folate. The tests were performed on Architect i2000SR (Abbott Diagnostics, USA). The presence of either low vitamin B12 or folate along with macrocytic RBCs qualified for a diagnosis of megaloblastic anemia.

The SPSS IBM V22 software (Chicago, USA) was used to analyze the results. Means and standard deviations were used to describe continuous variables, while frequency and percentages were used to describe categorical/discontinuous variables such as gender and age groups. The Chi-squared (χ^2) test was used to assess the correlation between

patients' measured characteristics with anemia and hypothyroidism status. An independent group's *t*-test was used to assess the categorical binary variable levels for statistically significant differences in the mean measured lab works and other continuous variables such as patient age. An adjusted *t*-test and Chi-squared test statistics and degrees-of-freedom (*df*) were quoted for each test. Moreover, multivariate binary logistic regression was employed to assess the combined and individual correlations between the patients' measured characteristics (gender, age, and lab results) with their odds of having anemia. The association between those predictor variables with anemia was expressed as an odds ratio as an effect size statistic. Multivariate model overall goodness-of-fit and accuracy were assessed using the Hosmer-Lemeshow test. The alpha statistical significance level was considered at 0.05 levels.

Results

Among the 100 patients who were included in the study, there were 52 women and 48 men. The range of age was 21–83, with a mean of 59 years. The MCV range was 100–129 fL (mean: 104.18 fL). Hct range was between 29.46–42.46% (mean: 35.96%). Of note, 53% of the cohort had low Hct value.

TSH levels ranged from .06 to 20.15 μ IU/mL (mean: 3.14 μ IU/mL). Eighteen patients (18%) had high TSH levels, qualifying for hypothyroidism. Among these, 11 (61%) were women and seven (39%) were men. The range of age was 22–85 years (mean 61.1). Eight patients (44%) had low Hct levels (overall range 16.2–45%, mean: 36%), while the MCV ranged between 100–118.3 fL (mean 105.8 fL). Finally, five patients (28%) and one patient (6%) had concomitant vitamin B12 and folate deficiencies, respectively.

The range of serum level for vitamin B12 was 48.2–2000 ng/mL (mean 375 ng/mL) and for folate was 1.7–20 ng/mL (mean 8.74 ng/mL) for the entire cohort. Megaloblastic anemia was evident in 27 patients (27%) as follows: isolated vitamin B12 deficiency in 13 patients (13%), isolated low folate in nine patients (9%), and a combined deficiency in five patients (5%). For those patients with megaloblastic anemia, 15 (56%) had low Hct (range 16.2–48.5%, mean: 34.3%), while MCV values ranged between 100–125 fL (mean 105.2 fL).

No statistically significant association was found between increased TSH level and gender ($p=.501$), age group ($p=.854$), hematocrit level ($p=.681$), vitamin B12 deficiency ($p=.437$) or folate deficiency ($p=.591$). Patients with high TSH tended to have higher than normal levels of vitamin B12 and folate, but this was not statistically significant ($p=.067$ and $p=.061$, respectively). Again, the mean MCV was not statistically different between high TSH cohort and vitamin B12 deficiency ($p=.551$) or folate deficiency ($p=.493$). Table 1 presents a summary of the overall clinical and laboratory results.

Further analysis showed that patients with low Hct levels had significantly higher MCV values than those of normal Hct ($p<.001$). Low Hct levels were more common in older patients (62.2 ± 16) than normal Hct (56.2 ± 17), but statistically not significant ($p=.074$). However, no correlation was found between the Hct level and the status of TSH, vitamin B12 and folate ($p=.093$). On multivariate analysis, patients above the age of eighty had significantly greater odds of having low Hct than those younger than forty. There was also a significant and positive correlation between vitamin B12 and folate levels ($p<.001$).

Discussion

Hypothyroidism is a common disease that affects 2–5% of the population all over the world [3]. The severity of symptoms and complications is variable according to the degree of hormone deficiency. The association between thyroid diseases and anemia is well documented in the literature and appears to be common in different geographic areas and populations, including Arabs [3–9]. Previous studies from Saudi Arabia showed a common association of hypothyroidism and anemia [10–11]. The high prevalence and common association indicate the tremendous health and financial impact on the general population.

There are multiple types of anemia that develop in hypothyroidism. Thyroid hormones have a direct stimulatory effect on the process of erythropoiesis in bone marrow, and an indirect effect through the release of erythropoietin from kidneys. Thus, the most commonly encountered anemia in hypothyroidism is the normocytic and normochromic type [3]. In addition, a hypochromic microcytic pattern can be seen. Patients with hypothyroidism have decreased iron absorption and women tend to have menorrhagia [12–13]. Moreover, iron deficiency can cause thyroid dysfunction and adding iron to levothyroxine would improve thyroid recovery [13].

Hypothyroidism is a notorious cause of macrocytic anemia and this occurs due to different factors. Hypothyroid patients commonly have inadequate nutrition due to loss of appetite and decreased gastrointestinal absorption of folate and vitamin B12. In addition, pernicious anemia is 20 times more common in hypothyroid patients, which results in vitamin B12 deficiency and the emergence of megaloblastic anemia [12]. Nevertheless, macrocytic RBCs can appear in

hypothyroidism as an adaptive change to decreased cellular metabolism without overt nutritional deficiency. Thus, the frequency of macrocytosis in hypothyroidism can be as high as 55% of cases [12].

This study viewed the relationship of macrocytic anemia with hypothyroidism from a different perspective. The frequency of hypothyroidism among patients with macrocytosis has rarely been investigated in the literature. Although hypothyroidism was less common than megaloblastic anemia, the results of this study revealed a comparable frequency. In addition, only 44% of hypothyroid patients had laboratory-evidenced anemia. This indicates that macrocytosis precedes the development of anemia and is a more sensitive test. In addition, Hct can rise in cases of dehydration, smoking, and hypoxia, potentially masking the overall picture of macrocytic anemia.

The results of our study also demonstrated that other causes of macrocytosis can coexist with hypothyroidism. Almost one third of hypothyroid patients in this study had deficiency in either vitamin B12 or folate. This is in agreement with the literature, as hypothyroidism can result in nutritional deficiencies [12,14]. This finding is also important for clinicians, especially in primary health care, as the presence of vitamin B12 or folate deficiencies in patients with macrocytosis does not rule out hypothyroidism as the definite cause.

In addition to megaloblastic anemia and hypothyroidism, other causes of macrocytic anemia include myelodysplastic syndrome, aplastic anemia, alcoholism, chronic liver disease and certain drugs [15–16]. The remaining cases in this study could potentially fall under these conditions if they had been specifically investigated. In two previous

studies, the frequency of hypothyroidism among macrocytic patients was 1–3.9% [17–18]. This study showed a higher frequency of 18%, which could be attributed to different epidemiology of disease and to the small cohort. Similar to our study, megaloblastic anemia was more common than hypothyroidism in these two studies. It is worth mentioning that a subset of patients with megaloblastic anemia may have a normal serum level of vitamin B12 and folate. More sensitive tests such as intra-RBC folate, serum methylmalonic acid and homocysteine levels, appear to be more reliable [16].

Conclusion

This study provides an overview of the prevalence of hypothyroidism in patients with macrocytosis. The results are important for physicians as a routine CBC test is commonly ordered in clinical practice. Megaloblastic anemia gains most of the attention when the MCV result is high, which could cause hypothyroidism to be missed. Testing serum TSH level is recommended in cases of macrocytosis, even if the patient has low vitamin B12 or folate levels or is not anemic. A significant number of patients would benefit from correct diagnosis and early treatment of hypothyroidism.

Table 1. Bivariate analysis of the association of serum TSH results with other clinical and laboratory findings (n=100)

Variables	High TSH	Non-High TSH	Statistical test (df)	p-value
Women	11 (61%)	41 (50%)	$\chi^2 (1) = .500$	.501
Men	7 (39%)	41 (50%)		
Age (years), mean (SD)	61.1 (16.8)	59.41 (16.9)	$t (98) = .185$	.854
20–40	1 (6%)	12 (15%)	$\chi^2 (3) = 1.740$	.629
40–60	7 (38%)	27 (33%)		
60–80	5 (28%)	34 (41%)		
>80	5 (28%)	9 (11%)		
Serum vitamin B12, mean	651 (651)	511.99 (446.6)	$t (98) = .530$	.437
Low	5 (28%)	18 (22%)	$\chi^2 (2) = 5.410$	.067
Normal	6 (33%)	56 (68%)		
High	7 (39%)	8 (10%)		
Serum folate level, mean (SD)	9.6 (5.80)	8.6 (6.83)	$t (98) = .540$	.591
Low	1 (6%)	12 (15%)	$\chi^2 (2) = 5.610$	.061
Normal	14 (78%)	53 (65%)		
High	3 (16%)	17 (20%)		
Hematocrit level, mean (SD)	36.6 (6.6)	35.85 (6.5)	$t (98) = .412$	.681
Non-anemic	8 (44%)	45 (56%)	$\chi^2 (2) = 1.020$	.313
Anemic	10 (56%)	37 (45%)		

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الهرمون المنبه للغدة الدرقية عند المرضى ذوي فقر الدم كبير الخلايا

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الملخص

الخلفية والأهداف: الهدف من هذه الدراسة هو فحص مدى شيوع قصور الغدة الدرقية بين المرضى المصابين بفقر الدم كبير الخلايا ومقارنتها مع مدى شيوع فقر الدم ضخّم الأرومات.

العينة والمنهجية: تم فحص العينات المنقولة بشكل روتيني لاختبار تعداد الدم الكامل إلى مختبر أمراض الدم في دراسة استباقية بحثاً عن حجم الخلية العالي، تم فحص مائة حالة مصابة بكبر الكريات لمعرفة مستويات هرمون الغدة الدرقية وفيتامين ب 12 ومستويات حمض الفولات. تم إجراء التحليل الإحصائي للتحقق من وجود ارتباط محتمل بين قصور الغدة الدرقية والمتغيرات الأخرى.

النتائج: كان هناك 52 امرأة و 48 رجلاً تراوحت أعمارهم بين 21 و 83 (متوسط 59 سنة). كان متوسط حجم خلايا الدم الحمراء 104.18 فيمتولتر، بينما كان متوسط خضاب الدم 35.96%. في المجمل، ثلاثة وخمسون (53%) مريضاً كانوا يعانون من فقر الدم. كان لدى ثمانية عشر (18%) مريضاً مستوى الهرمون المنبه للغدة الدرقية أعلى من المعدل الطبيعي، من بين هؤلاء، كان لدى ثمانية مرضى (44%) انخفاض في مستوى خضاب الدم و لدى ستة (33%) فقر الدم ضخّم الأرومات المصاحب. لم تظهر علاقة إحصائية ملموسة بين وجود مستوى مرتفع للهرمون المنبه للغدة الدرقية مع الجنس أو العمر أو مستويات فيتامين ب 12 أو حمض الفولات أو خضاب الدم.

الاستنتاجات: يحدث قصور الغدة الدرقية بشكل شائع في المرضى الذين يعانون من كبر خلايا الدم الحمراء بشكل مشابه لفقر الدم ضخّم الأرومات بل ويمكن أن يحدث كلاهما في وقت واحد. نوصي باختبار مستوى الهرمون المنبه للغدة الدرقية بشكل روتيني عند المرضى الذين لديهم كريات الدم كبيرة الحجم حتى لو كان مستوى خضاب الدم طبيعياً أو كانوا مصابين بفقر الدم ضخّم الأرومات.

الكلمات الدالة: قصور الغدة الدرقية، فقر الدم، تضخم خلايا الدم الحمراء، الهرمون المنبه للغدة الدرقية، فقر الدم ضخّم الأرومات.