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Evaluation of the prevalence and laboratory test results of overt thyrotoxicosis cases

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Abstract

Background: The frequency of thyrotoxicosis may vary between countries and some laboratory test results may be used in etiology research. This study aimed to evaluate the prevalence of thyrotoxicosis diagnoses and laboratory test results.

Methods: 3246 patients with overt thyrotoxicosis were included in this study. Laboratory test results, epicrisis, thyroid ultrasonography, thyroid scintigraphy, and radioactive iodine uptake test reports of the patients were examined in the study.

Results: Thyrotoxicosis was found due to levothyroxine overdose in 58.1% of the patients. When this group was excluded, 36.1% of the patients were diagnosed with toxic multinodular goiter most frequently. TRab levels were 8.5 times higher in Graves' disease than in other diagnostic groups. Anti-TPO levels were found to be the highest in the Graves' disease and Hashitoxicosis groups compared to other diagnostic groups ($p<0.001$). Anti-Tg levels were found to be highest in Graves' disease, Postpartum thyroiditis, and Hashitoxicosis patients ($p<0.001$). The free triiodothyronine / free thyroxine ratio was significantly higher, a cut-off value of >2.94 provided a sensitivity of 66% and specificity of 64% in diagnosing Graves' disease.

Conclusion: The causes of thyrotoxicosis show some differences between countries. Patients using levothyroxine should be informed about drug use and dose titration. The free triiodothyronine / free thyroxine ratio can be used in addition to other tests during diagnosis.

Keywords: thyrotoxicosis, thyroid antibodies, graves disease, hashitoxicosis, toxic nodular goiter.

What is new? What is important?

The most common etiology of patients with thyrotoxicosis detected in laboratory tests is the use of overdose levothyroxine therapy, which is important to be more careful when warning patients. Frequencies of causes of thyrotoxicosis may vary. While the most common cause is Graves' disease in many sources, TMNG was detected in this study.

INTRODUCTION

Thyrotoxicosis refers to excess thyroid hormones for any reason. There are suppressed thyroid stimulant hormone (TSH) (<0.4 microU/ mL), high free thyroxine (fT4), and/ or free triiodothyronine (fT3) in overt hyperthyroidism. Radioactive Iodine (RAI) uptake tests are used in the evaluation of the etiology. The causes of thyrotoxicosis are divided into two classes according to normal or increased and decreased RAI uptake. Normal or increased RAI uptake is observed in patients with Graves' disease (GD), toxic multinodular goiter (TMNG), toxic adenoma (TA), increased chorionic gonadotropin (ICG), TSH secreting pituitary adenoma and thyroid hormone resistance. Decreased RAI uptake is observed in patients with silent thyroiditis (ST), hashitoxicosis (HT), subacute thyroiditis (SAT), amiodarone-induced thyroiditis (AIT), iatrogenic thyrotoxicosis, levothyroxine overdose (LO), struma ovarii, acute thyroiditis and thyroid malignancies (TM) [1].

It is important to determine the etiology for the appropriate treatment of thyrotoxicosis. Antithyroid drugs (ATD), RAI treatment, and thyroidectomy can be used in GD, depending on the clinical conditions [2]. Since remission with ATDs is rare in patients with TA or TMNG, thyroidectomy or RAI treatment is recommended [3]. In patients with toxic nodular goiter, ATDs are used to render the patient euthyroid before surgery or RAI treatment. If there is a contraindication for

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the surgery, RAI treatment, or if the patient's life expectancy is short; ATDs can rarely be used as a long-term treatment [4]. Thyrotoxicosis due to thyroiditis is usually transient and beta-blockers (BB) can be used if symptomatic. In SAT, non-steroidal anti-inflammatory drugs (NSAID) and glucocorticoids can be used to help with pain and inflammation [5].

Thyrotoxicosis can lead to severe complications, including delirium and mental status disorders, osteoporosis, muscle weakness, arrhythmia, heart failure, thromboembolic events, cardiovascular collapse, and deaths. In this study, it is aimed to evaluate the prevalence of thyrotoxicosis, treatment methods, and laboratory test results.

MATERIAL AND METHOD

ETHICAL CONSIDERATIONS

The study was started once approval was obtained from the institutional clinical research ethics committee (approval number: 2034/2018, date: 07.06.2018) and carried out according to the ethical principles of the Declaration of Helsinki.

STUDY POPULATION AND DESIGN

All patients with TSH value <0.4 μIU/mL, regardless of gender, aged ≥18 years, who applied to the internal medicine and endocrinology outpatient clinic or service of a tertiary training and research hospital between 2014 and 2018 years for any reason were included in the study. The study was conducted retrospectively, using hospital automation data with the consent of the participants. Among a total of 11,814 patients with TSH value <0.4 μIU/mL, 3246 patients with high fT4 and/ or fT3 levels were included in the study.

In this study, serum TSH, fT4, fT3, antithyroid peroxidase (anti-TPO), antithyroglobulin (anti-Tg), TRab levels, fT3/fT4 ratio, prescription and epicrisis information, thyroid ultrasonography, scintigraphy, and RAI uptake tests were examined.

Overt thyrotoxicosis was diagnosed and divided groups as recommended in the thyroid disease diagnosis and treatment guideline of the Turkish Endocrine and Metabolism Society (TEMD) 2023 thyroid study group [1].

STATISTICAL ANALYSIS

Data analysis was done with Statistical Package for Social Sciences (SPSS) 20 program for Windows. The normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Categorical variables are expressed as numbers and percentages. The difference of numerical variables according to the diagnosis groups was evaluated with Kruskal Wallis analysis. Roc curve analysis was performed for the cut-off value of the fT3/fT4 ratio. Spierman's rho test was performed to evaluate the relationship of the fT3/fT4 ratio with laboratory test results. The $p< 0.05$ value was accepted as significant in statistical analysis.

RESULTS

The age of the patients was found 51±15 (18–98) years. 81.1% (n=2631) were female, and 18.9% (n=615) were male. Thyrotoxicosis due to LO was found in 58.1% (n=1886) of the patients.

When thyrotoxicosis cases due to LO were excluded, it was seen that TMNG was diagnosed most frequently in 36.1% of the patients. This was followed by GD, SAT, ICG, ST, TA, CE (iodinated contrast agent exposure), HT, TM, AIT, and PT (postpartum thyroiditis) diagnoses (Table I).

Thyrotoxicosis causes differ according to the genders ($p<0.001$). Only the frequency of AIT and CE were seen more frequently in males, other diagnosis groups were found to be more common in females.

There was a significant difference in the relationship between the causes of thyrotoxicosis and age ($p<0.001$). Only CE was found more common in the ≥65 years group (Table II).

Excluding thyrotoxicosis patients due to LO; medical treatment for 57.7% (n=785), surgical treatment for 19.8% (n=269), RAI treatment for 11.6% (n=158), and non-iodized salt for 11.1% (n=148) of patients were recommended. Methimazole (MM) was preferred in 38.7% of medical treatments, followed by propylthiouracil (PTU) in 18.0%, NSAIDs in 15.2%, BB in 12.4%, MM+BB combination in 12.1%, PTU+BB combination in 3.2%, steroid treatment in 0.3% were observed. It was seen that; MM was most frequently prescribed in the medical treatment of GD, TMNG, and TA. PTU was the most common in the medical treatment of ICG. NSAIDs were most frequently prescribed in SAT and BB was most frequently prescribed in ST, HT, AIT, and PT patients. It was observed that 74.5% of those diagnosed with GD received medical treatment, 13.3% by RAI treatment, and 12.2% by surgical treatment. 44.8% of TMNG patients were receiving medical treatment,

37.5% surgical treatment, and 17.7% RAI treatment. 82.4% of HT patients, 99.2% of SAT, and 83.4% of AIT were receiving medical treatment. 55.0% of ICG patients were treated with non-iodized salt and 45.0% medical treatment. 70.4% of ST patients, 85.0% of CE, and 91.7% of PT patients were treated with non-iodized salt.

Considering the relationship between laboratory test results and diagnostic groups, TSH levels were found to be significantly suppressed in GD compared to TMNG and ICG ($p<0.001$). fT4 levels were found to be significantly higher in SAT, HT, AIT, and PT compared to others ($p<0.001$). fT3 was found to be significantly higher in GD and lower in LO compared to other groups ($p<0.001$). TRab levels were 8.55 times higher in GD patients than in other diagnostic groups (95% CI 5.8–12.5) ($p<0.001$). Anti-TPO levels were found to be the highest in the GD and HT groups compared to other diagnostic groups ($p<0.001$) and there was no significant difference between these two groups ($p=1.00$). Anti-TPO levels were found to be high in 93.3% of HT patients and 72.7% of GD patients. Anti-Tg levels were found to be highest in GD, PT, and HT patients ($p<0.001$). Anti-Tg levels were found to be high in 66.7% of HT patients, 48.6% of GD patients, and 33.3% of PT patients (Table III). Additionally, a significant relationship was observed between the diagnostic groups and the fT3/fT4 ratio ($p<0.001$). The highest median value of the fT3/fT4 ratio (3.28) was found in GD patients, while the lowest median value (1.70) was noted in AIT cases. Notably, the fT3/fT4 ratio was significantly higher in GD compared to others. A cut-off value of >2.94 for this ratio provided a sensitivity of 66% and specificity of 64% in diagnosing GD (Area Under the Curve=0.647, $p<0.001$) (Figure 1).

Table I

Prevalence of thyrotoxicosis causes (excluding LO)

DIAGNOSIS	n	%
GD	427	31.4%
TMNG	491	36.1%
TA	65	4.8%
ICG	100	7.4%
ST	81	6.0%
HT	17	1.2%
SAT	120	8.8%
CE	20	1.5%
AIT	12	0.9%
TM	15	1.1%
PT	12	0.9%

Graves' disease (GD), toxic multinodular goiter (TMNG), toxic adenoma (TA), increased chorionic gonadotropin (ICG), silent thyroiditis (ST), hashitoxicosis (HT), subacute thyroiditis (SAT), iodinated contrast agent exposure (CE), amiodarone- induced thyroiditis (AIT), thyroid malignancies (TM), postpartum thyroiditis (PT), levothyroxine overdose (LO).

Table II

Distribution of thyrotoxicosis causes by age

Diagnosis	<65 years		≥65 years		p
	n	%	n	%	
GD	387	90.6%	40	9.4%	**< 0.001***
TMNG	321	65.4%	170	34.6%	
TA	37	56.9%	28	43.1%	
ICG	100	100.0%	0	0%	
ST	70	86.4%	11	13.6%	
HT	15	88.2%	2	11.8%	
SAT	115	95.8%	5	4.2%	
CE	7	35.0%	13	65.0%	
AIT	10	83.3%	2	16.7%	
TM	12	80.0%	3	20.0%	
PT	12	100.0%	0	0%	
LO	1520	80.6%	366	19.4%	

*p<0,05 is considered significant for statistical analyses. Graves' disease (GD), toxic multinodular goiter (TMNG), toxic adenoma (TA), increased chorionic gonadotropin (ICG), silent thyroiditis (ST), hashitoxicosis (HT), subacute thyroiditis (SAT), iodinated contrast agent exposure (CE), amiodarone- induced thyroiditis (AIT), thyroid malignancies (TM), postpartum thyroiditis (PT), levothyroxine overdose (LO)

Table III

The relationship between laboratory test results and diagnostic group

	GD **Median (IQR)**	**TMNG** **Median (IQR)**	**TA** **Median (IQR)**	**ICG** **Median (IQR)**	**ST** **Median (IQR)**	**HT** **Median (IQR)**	**SAT** **Median (IQR)**	**CE** **Median (IQR)**	**AIT** **Median (IQR)**	**TM** **Median (IQR)**	**PT** **Median (IQR)**	**LO** **Median (IQR)**	**p*** **value**
TSH (µIU/mL)	0.02(0.01-0.05)	0.04(0.02-0.12)	0.03(0.02-0.06)	0.07(0.03-0.1)	0.04(0.01-0.07)	0.03(0.01-0.05)	0.03(0.01-0.06)	0.05(0.01-0.14)	0.02(0.01-0.66)	0.06(0.03-0.14)	0.02(0.02-0.05)	0.09(0.04-0.18)	**<.001**
fT4 (ng/dL)	1.8(1.36-3.10)	1.46(1.2-2.08)	1.6(1.15-1.92)	1.56(1.23-1.9)	1.55(1.3-2.15)	1.98(1.45-2.98)	2.20(1.67-3.24)	1.51(1.3-2.07)	2.14(1.89-2.28)	1.60(1.37-1.99)	1.91(1.35-2.59)	1.44(1.26-1.80)	**<.001**
fT3 (ng/dL)	5.88(4.30-9.8)	4.31(3.42-5.5)	4.8(3.94-5.94)	4.30(3.8-4.95)	4.57(3.98-5.81)	5.10(4.26-6.7)	5.06(4.28-7.3)	3.63(3.05-4.36)	3.86(2.87-4.35)	4,223.75-4.64)	4.99(4.1-7.8)	3.40(3.05-4.04)	**<.001**
AntiTPO (IU/mL)	140(10.3-516)	3.50(0.70-61)	2.6(0.6-13.3)	1.35(0.5-12.0)	2.70(0.7-11.5)	146(65-798)	2.50(0.7-13.2)	1.60(0.7-13.6)	2.7(0.6-31.0)	0.95(0.4-16.0)	7.6(2.05-192.7)	16.7(1.6-283.0)	**<.001**
AntiTg (IU/mL)	13.2(2,1-110)	2.10(0.9-10.2)	2.1(1.15-10.0)	2.50(0.7-11.4)	3.15(0.9-23.7)	17.6(4.5 8-121)	3.60(0.8-24.4)	9.00(0.85-11.2)	5.5(1.0-11.0)	9.20(2.1-18.0)	31.9(2.4-222.0)	2.10(0.8-12.58)	**<.001**
TRab (U/L)	10(5.54-24.4)	6.14(4.2-11.1)	6.03(3.99-9.26)	5.38(3.4-7.8)	4.80(3.73-6.9)	7.08(6.0-10.7)	4.55(3.1-6.68)	5.23(3.8-8.53)	5.8(2.09-8.89)	7.32(7.32-7.32)	3.4(2.81-9.6)	6.13(4.15-9.95)	**<.001**
fT3/fT4	3.28(2.7-4.0)	2.9(2.3-3.6)	3.1(2.6-4.4)	2.7(2.4-3.3)	2.82(2.2-3.3)	3.08(2.47-3.55)	2.35(1.97-2.8)	2.17(1.7-2.70)	1.7(1.6-2.56)	2.43(2.4-3.06)	2.9(2.5-3.4)	2.42(2.0-2.82)	**<.001**

*p<0,05 is considered significant for statistical analyses. Thyroid stimulant hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), antithyroid peroxidase (anti TPO), antithyroglobulin (anti Tg), TSH receptor antibody (TRab), free Triiodothyronine (fT3), free thyroxine (ft4), Graves' disease (GD), toxic multinodular goiter (TMNG), toxic adenoma (TA), increased chorionic gonadotropin (ICG), silent thyroiditis (ST), hashitoxicosis (HT), subacute thyroiditis (SAT), iodinated contrast agent exposure (CE), amiodarone- induced thyroiditis (AIT), thyroid malignancies (TM), postpartum thyroiditis (PT), levothyroxine overdose (LO).

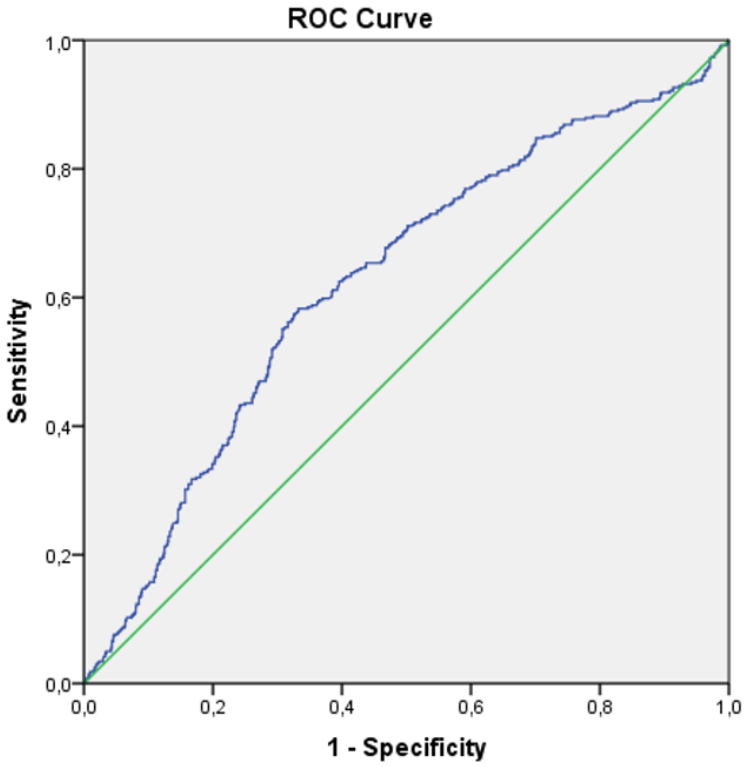


Figure 1. Roc curve analysis of the free triiodothyronine / free thyroxine ratio for the diagnosis of Graves' disease.

DISCUSSION

In the United States, the prevalence of hyperthyroidism is approximately 1.2% (0.5% overt and 0.7% subclinical); the most common causes are GD, TMNG, and TA [6]. In Africa, 54% of thyrotoxicosis cases are caused by GD, 39% by TMNG, 10% by TA, 2% by thyroiditis and 1% by other rare causes [7]. TMNG is responsible for 51.4% of thyrotoxicosis cases, followed by HT with 16.7%, GD with 8.3%, TA with 5.6%, and SAT with 2.7% in a study conducted in Turkey[8]. [8]. In a study, the incidence of AIT was found to be 9.5% [9]. In another study, the incidence of AIT was from 0% to 9%, with a higher incidence in iodine-deficient countries [10]. The frequency of thyrotoxicosis was found to be 9.6% in participants using thyroid hormone, while 0.8% in non-hormone users [11]. Within this study, the most common diagnosis among patients was TMNG, accounting for 36.1% of cases. This was followed by GD, SAT, ICG, ST, TA, CE, HT, TM, AIT, and PT. In a study, the prevalence of iodine deficiency was found to be the lowest (10.1%) in America and the highest (59.9%) in Europe [12]. On the other hand, it has been shown that the prevalence of TMNG and TA increases with aging in regions with iodine deficiency [6,13]. The reason why TMNG was more than GD in this study may be because our country is a region with iodine deficiency and the mean age was 51±15 years.

When treatment options are evaluated, RAI is the first choice for GD in the United States, whereas ATDs are the primary treatment approach in England [14]. A study revealed that 45% of thyrotoxicosis patients were treated with ATD, 36% with RAI, and 18% with surgical treatment [15]. In this study, it was observed that 57.7% of patients recommended medical treatment, 19.8% surgical treatment, 11.6% RAI, and 11.1% non-iodized salt.

Thyroid ultrasonography, scintigraphy, RAI uptake test, and laboratory test results play a crucial role in the diagnosis of thyrotoxicosis. TRab positivity can diagnose GD with 98% sensitivity and 99% specificity. Anti-TPO was found to be positive in approximately 75% [16]. In this study, TRab levels were 8.55 times higher in GD patients than in other diagnostic groups. Anti-TPO levels were found to be high in 93.3% of HT patients and 72.7% of GD patients. Anti-Tg levels were found to be highest in GD, PT, and HT patients.

In a study comparing patients with SAT and healthy individuals, fT4/fT3 ratios were found to be significantly higher than in healthy individuals [17]. In another study, the fT3/fT4 ratio was 71.7% sensitivity and 88.6% specificity, and the cut-off value was 2.96 for GD, and it was recommended to use the fT3/fT4 ratio for the differential diagnosis of GD in cases where RAI uptake test and TRab level couldn't be measured [18]. In this study, a significant relationship was observed between the diagnostic groups and fT3/fT4 ratios. A cut-off value of fT3/fT4 >2.94 in GD provided 66% sensitivity and 64% specificity.

CONCLUSION

Thyrotoxicosis, whose clinical manifestations range from mild symptoms to thyroid storm, is to be diagnosed quickly and receive appropriate treatment. This study showed that LO is the most common cause in thyrotoxicosis cases and draws attention to the careful adjustment of the levothyroxine dose and warnings about drug use. The causes and treatment methods of thyrotoxicosis show some differences between countries. In cases where GD is suspected, checking the fT3/fT4 ratio may be helpful in addition to other tests.

Context: Frecvența tireotoxicozei poate varia de la o țară la alta și unele rezultate ale testelor de laborator pot fi utilizate pentru cercetarea etiologică. Acest studiu și-a propus să evalueze prevalența diagnosticelor de tireotoxicoză și rezultatele testelor de laborator.

Metode: 3246 de pacienți cu tirotoxicoză au fost incluși în acest studiu. Rezultatele testelor de laborator, epicriza, ecografia tiroidiană, scintigrafia tiroidiană și rapoartele de captare a iodului radioactiv ale pacienților au fost evaluate.

Rezultate: Tirotoxicoza a fost găsită din cauza supradozajului cu levotiroxină la 58,1% dintre pacienți. Când acest grup a fost exclus, 36,1% dintre pacienți au fost cel mai frecvent diagnosticați cu gușă multinodulară toxică. Nivelurile TRb au fost de 8,5 ori mai mari în boala Graves decât în alte grupuri de diagnostic. Nivelurile anti-TPO s-au dovedit a fi cele mai ridicate în grupurile cu boala Graves și hashitoxicoză în comparație cu alte grupuri de diagnostic ($p<0,001$). Nivelurile anti-Tg s-au dovedit a fi cele mai ridicate la pacienții cu boala Graves, tiroidita postpartum și hashitoxicoză ($p<0,001$). Raportul triiodotironină liberă/tiroxină liberă a fost semnificativ mai mare, o valoare prag de peste 2,94 a furnizat o sensibilitate de 66% și o specificitate de 64% în diagnosticarea bolii Graves.

Concluzie: Cauzele tireotoxicozei arată unele diferențe între țări. Pacienții care utilizează levotiroxină trebuie informați despre utilizarea medicamentelor și titrarea dozei. Raportul triiodotironină liberă/tiroxină liberă poate fi utilizat în plus față de alte teste în timpul diagnosticului.

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