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Clinical Aspects of Thyrotoxicosis in 592 Patients: A Single Center Experience from Turkey

Beş Yüz Doksan İki Tirotoksikozu olan Hastanın Klinik olarak Değerlendirilmesi: Tek Merkez Deneyimi

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Abstract

Purpose: To determine the main causes of thyrotoxicosis and to compare the clinical and biochemical fetaures of the patients according to the underlying cause of thyrotoxicosis.

Material and Method: Five hundred ninety-two patients, who were consecutively diagnosed with thyrotoxicosis, were retrospectively analysed. Symptoms of thyrotoxicosis, serum thyroid-stimulating hormone (TSH), free T3 and free T4 levels, anti-thyroglobulin autoantibody (TGAb), anti-thyroid peroxidase autoantibody (TPOAb) and ultrasonographic features were recorded. To determine the cause of thyrotoxicosis, Tc-99m pertechnetate thyroid scintigraphy was performed in all patients except for pregnant women. The clinical and biochemical results were compared between the patients with different diagnosis of thyrotoxicosis.

Results: 40.9% of patients were diagnosed with toxic multinodular goiter (TMNG). The other main causes of thyrotoxicosis were: Graves' disease (GD) (22%), thyroiditis (14.8%), gestational thyrotoxicosis (12.7%), and toxic adenoma (9.6%). The clinical presentation and severity of thyrotoxicosis varied according to the underlying cause. Weight loss was more frequently observed in patients with GD (p=0.0001), while cardiac arrhythmia dominated in patients with TMNG (p=0.0001). Moderate (27%) or severe (23.9%) thyrotoxicosis was more common in patients with GD than in patients with other forms of thyrotoxicosis (p=0.0001).

Discussion: Toxic multinodular goiter is the most common cause of thyrotoxicosis in our region. *Turk Jem 2014; 18: 121-125*

Key words: Thyrotoxicosis, toxic multinodular goiter, Graves's disease

Conflict of interest: The authors reported no conflict of interest related to this article.

Özet

Amaç: Tirotoksikozun ana nedenlerini belirlemek ve altta yatan sebeplere göre hastaların klinik ve biokimyasal özelliklerini karşılaştırmak idi.

Gereç ve Yöntem: Ardışık olarak tirotoksikoz tanısı alan 592 hastanın verileri retrospektif olarak incelendi. Tirotoksikoz semptomları, TSH, serbest T3, serbest T4, antiTG ve antiTPO düzeyleri ile ultrasonografi özellikleri kaydedildi. Tirotoksikozun nedenini saptamak için tüm hastalara Tc99m pertechnetate tiroid sintigrafisi çekildi. Hastaların klinik ve biokimyasal sonuçları tirotoksikoz nedenlerine göre karşılaştırıldı.

Bulgular: Hastaların %40,9'una toksik multinodüler guatr (TMNG) tanısı kondu. Tirotoksikozun diğer ana nedenleri: %22 Graves hastalığı, %14,8 tiroidit, %12,7 gestasyonel tirotoksikoz ve %9,6 toksik adenom idi. Tirotoksikozun klinik prezentasyonu ve ciddiyeti altta yatan nedene göre değişiyordu. Kardiak aritmi TMNG'li hastalarda daha sık görülürken (p=0,0001), kilo kaybı Graves hastalığı olanlarda daha fazlaydı (p=0,0001). Orta (%27) ya da ağır (%23,9) tirotoksikoz Graves hastalığı olanlarda daha yaygındı (p=0,0001).

Tartışma: Toksik multinodüler guatr bizim bölgemizde tirotoksikozun en sık nedenidir. *Turk Jem 2014; 18: 121-125*

Anahtar kelimeler: Tirotoksikoz, toksik multinodüler guatr, Graves hastalığı

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Introduction

Thyrotoxicosis, defined as elevated free thyroxine (fT4) and/or free triiodothyronine (fT3) levels, is a well recognized clinical entity, but at present, little information is available concerning the prevalence of the disorders that produce it. Several different disorders can cause thyrotoxicosis. It is essential to determine the correct cause, because appropriate therapy depends upon the underlying mechanism of thyrotoxicosis.

The studies, evaluating the distribution of disorders that cause thyrotoxicosis in different regions of the world, were performed during the years 1980-1990. Graves' disease (GD) is the most common cause of thyrotoxicosis, accounting for 60 to 80% of all cases in different regions of the world (1,2,3,4,5,6). Most of the remaining causes are toxic multinodular goiter, toxic adenoma, exogenous thyroid hormone administration, gestational thyrotoxicosis, and several types of thyroiditis. Toxic multinodular goiter (TMNG) may be more common than GD in older patients from areas where iodine intake is relatively low (7). After 1990s, there is little information about the clinical spectrum of thyrotoxicosis in the literature.

The clinical manifestations of thyrotoxicosis can vary considerably among patients. Age of the patient, duration of illness, elevation in serum levels of fT4 and fT3, and presence of comorbid conditions can affect the clinical features of patients (8). Both overt and subclinical disease may lead to characteristic signs and symptoms. The underlying cause of thyrotoxicosis may have an effect on the clinical presentation of patients. Factitious thyrotoxicosis is more common than GD as the cause of subclinical thyrotoxicosis (9).

In this setting, the aim of this study was to determine the main causes of thyrotoxicosis. Secondly, we aimed to determine the clinical and biochemical fetaures of patients and compare according to the underlying cause of thyrotoxicosis.

Materials and Methods

This retrospective study included all consecutive patients who attended our endocrinology outpatient clinic for thyrotoxicosis between November 2011 and November 2012. This study was approved by the local ethical committee. This is the only endocrinology center in Rize, province of the eastern part of Black Sea in Turkey with about 150.000 inhabitants. Five hundred ninety-two patients were diagnosed with thyrotoxicosis by suppressed serum thyrotropin (TSH) levels during a period of one year. The institutional medical ethics committee approved the study and all patients were enrolled after providing written informed consents. Patients who received exogenous thyroid hormone were excluded from the study. Medical records of patients were reviewed and the following information at the time of diagnosis was recorded: patient's age, gender, presence or absence of symptoms of thyrotoxicosis such as weight loss, heat intolerance, tremor, palpitations and nervousness, thyroid gland size, presence or absence of thyroid tenderness, symmetry, and nodularity, presence or absence of cardiac arrhythmia (documented by electrocardiography), and serum TSH, fT3 and fT4 levels.

To determine the cause of thyrotoxicosis, Tc-99m pertechnetate thyroid scintigraphy was performed in all patients except for pregnant women. Ultrasonographic examination was also done and the echogenicity of the thyroid parenchyma and the size, number, location and structure of nodules were recorded. Serum levels of anti-thyroglobulin autoantibody (TGAb), anti-thyroid peroxidase autoantibody (TPOAb) and TSH receptor- stimulating autoantibody (TSHRAb) were recorded.

The patients were diagnosed with GD, TMNG, toxic adenoma (TA), thyroiditis or gestational thyrotoxicosis. The diagnosis of GD was based on a diffuse high uptake of radioactive iodine and high serum concentrations of TSHRAb. TA was defined as thyroid nodule which demonstrated uptake with suppressed uptake in the surrounding thyroid tissue on thyroid scintigraphy. TMNG was defined as multiple thyroid nodules on thyroid ultrasonography and one or more focal areas of increased radioiodine uptake on thyroid scintigraphy. The diagnosis of thyroiditis was based on a low uptake of radioactive iodine. Erythrocyte sedimentation rate (ESR) and C-reactive protein levels were measured in patients whose thyroid gland was hard and painful on palpation to distinguish subacute thyroiditis from the other causes of thyroiditis. Gestational thyrotoxicosis was defined as transient hyperthyroidism, limited to the 1st half of pregnancy, and characterized by elevated fT4 and suppressed or undetectable serum TSH and normal echogenicity of thyroid parenchyma on ultrasonography, in the absence of serum levels of thyroid autoantibodies.

TSH, fT3, fT4, TGAb, and TPOAb concentrations were measured using chemiluminescent microparticle enzyme immunoassay (CMIA) method (Abbott Architect i2000 (Abbott Diagnostic, USA). TSHRAb levels were measured using radioimmunoassay (RIA) method with gamma counter.

Statistical Analysis

Data were analyzed using SPSS Software version 17, for Windows (SPSS, Inc. Chicago, IL, USA). Results were expressed as mean ± standard error of means. Differences among the groups not showing normal distribution were analyzed by the Kruskal-Wallis test. Dual comparisons among groups with significant values were evaluated with the Bonferroni adjusted Mann-Whitney U test. Chi-square test was used to compare categorical variables. A p value of less than 0.05 was considered statistically significant.

Results

Between November 2011 and November 2012, 592 patients were diagnosed with thyrotoxicosis by suppressed serum TSH levels and these patients consisted of 448 (75.7%) women and 144 men (24.3%) with a mean age of 50.48±17.68 years (range:16-94 years) (Table 1). 25.5% of patients were older than 65 years. Thyrotoxicosis was more common in women than in men (3:1 ratio).

Two hundred forty-two of 592 patients (40.9%) were diagnosed with TMNG. The other main causes of thyrotoxicosis were: GD (22%), thyroiditis (14.8%), gestational thyrotoxicosis (12.7%), and TA (9.6%) (Table 1). TA and TMNG were more common in older people compared to GD, thyroiditis and gestational thyrotoxicosis ($p<0.001$) (Table 2). The patients with TMNG were older than patients with TA ($p<0.001$), GD ($p<0.001$) and thyroiditis ($p<0.001$). The mean age of patients with GD and thyroiditis were similar ($p=0.622$). GD was the most common cause of thyrotoxicosis (49.2%) in second and

third decades of life and rare after 60 years of age (7%). TMNG was diagnosed in 74.5% of patients older than 60 years.

The clinical presentation of thyrotoxicosis varied according to the underlying cause (Table 2). The major proportion of patients with GD had the classical signs of thyrotoxicosis, such as nervousness, weight loss despite increased appetite, palpitations, tremor and heat intolerance, while the other patients were oligosymtomatic. Weight loss was more frequently observed in patients with GD (p<0.001), while cardiac arrhythmia dominated in patients with TMNG (p<0.001). Palpitations, heat intolerance, nervousness, tremor and weight loss (but not cardiac arrhythmia) were significantly more frequent among patients whose TSH levels were below 0.1 uIU/mL compared to patients with the levels of 0.1-0.4 uIU/mL (p<0.001). Patients older than 65 years had less nervousness, heat intolerance and weight loss, but had more cardiac arrhythmia compared with younger subjects (<50 years) (p<0.001). Palpable goiter was present in 69% of patients.

The severity of thyrotoxicosis differed according to the underlying cause (p<0.001). Among all subjects, 49% had subclinical thyrotoxicosis. Moderate (27%) or severe (23.9%) thyrotoxicosis was more common in patients with GD than in patients with other forms of thyrotoxicosis. The other causes of thyrotoxicosis presented with subclinical or mild thyrotoxicosis in majority of the patients (Table 3). Serum levels of fT3 and fT4 were significantly higher in patients with GD than in patients with TMNG (p<0.001, p<0.001), TA (p<0.001, p<0.001), thyroiditis (p<0.001, p=0.001), and gestational thyrotoxicosis (p<0.001, p=0.001), respectively. There were no significant differences between patients with TA and TMNG in terms of fT3 and fT4 levels (p=0.116, p=0.797, respectively). Patients with thyroiditis had higher fT3 and fT4 levels compared to patients with TA (p=0.023) and TMNG (p=0.005). Levels of TSH in patients with GD were significantly lower than in patients with TMNG (p<0.001), TA (p<0.001), thyroiditis (p<0.001) and gestational thyroiditis (p<0.001). Nevertheless, there were no significant differences in TSH levels between patients with TA, TMNG, thyroiditis, and gestational thyrotoxicosis (p>0.05).

TSHRAb levels were detectable in 58.9% of patients with GD (Table 3). These ratios were 63% and 65.3% for TPOAb and TGAb,

Table 1. Causes of thyrotoxicosis

Type of thyrotoxicosis	All patients (n=592)	Patients between 2. and 3. decades (n=126)	Patients between 4. and 5. decades (n=191)	Patients over 6. decade (n=200)
Graves' disease	22% (130)	49.2% (62)	28.3% (54)	7% (14)
Toxic adenoma	9.6% (57)	6.4% (8)	16.2% (31)	9% (18)
Toxic multinodular goiter	40.9% (242)	7.9% (10)	43.5% (83)	74.5% (149)
Thyroiditis Painless thyroiditis Subacute thyroiditis	14.8% (88) 76.1% (67) 23.9% (21)	36.5% (46)	12% (23)	9.5% (19)
Gestational thyrotoxicosis	12.7% (75)	-	-	-

The cases with gestational thyrotoxicosis were not included in the statitical analysis of the proportion of patients according to the decades.

Table 2. Clinical presentation of the patients with thyrotoxicosis

Parameter	Graves' disease n=130	Toxic adenoma n=57	Toxic multinodular goiter n=242	Thyroiditis n=88	Gestational thyrotoxicosis n=75	p
Age ± SEM	41.08±1.182	54.46±1.72	63.29±0.84	43.10±1.73	31.07±0.57	<0.001*
Gender (female %)	77.7% (101)	64.9% (37)	71.5% (173)	71.5% (63)		0.315**[a]
Weight loss (%)	29.2% (38)	3.5% (2)	3.3% (8)	4.5% (4)	6.6% (5)	<0.001**
Nervousness (%)	72.3% (94)	29,8% (17)	34.3% (83)	34.1% (30)	12% (9)	<0001**
Heat intolerance (%)	73.8% (96)	33.3% (19)	37.1% (90)	32.9% (29)	16% (12)	<0.001**
Tremor (%)	56.1% (73)	26.3% (15)	23.5% (57)	14.7% (13)	6.6% (5)	<0.001**
Palpitation (%)	54.6% (71)	33.3% (19)	35.5% (86)	28.4% (25)	18.6% (14)	<0.001**
Cardiac arrhythmia (%)	0.7% (1)	8.7% (5)	19.4% (47)	2.2% (2)	1.3% (1)	<0.001**

Values are expressed as means ± SEM
*Kruskal Wallis **Chi square test
[a]: The cases with gestational thyrotoxicosis were not included in the statitical analysis

respectively. Both TGAb and TPOAb positivity was determined in 46.2% of patients with Graves' thyrotoxicosis. The percentage of TGAb-positive subjects was found to be 58.6% in patients with thyroiditis and 26.4% in patients with TMNG, and that of TPOAb-positive subjects was 29.8% in thyroiditis and 17.1% in TMNG group (Table 3). Thyroid autoantibodies were not measurable in most of the patients with TA and TMNG. Levels of TGAb and TPOAb were significantly higher in patients with GD than in patients with TA (p<0.001, p<0.001), TMNG (p<0.001, p<0.001) and gestational thyrotoxicosis (p<0.001, p<0.001). While serum levels of TGAb were similar in patients with GD and thyroiditis (p=0.680), TPOAb levels were higher in patients with GD than in patients with thyroiditis (p<0.001). As expected, thyroid autoantibody positivity was higher among patients with GD when compared to those with the other causes of thyrotoxicosis; and the difference was significant (p<0.001).

Thyroid nodules were observed on ultrasonography in 402 (67.9%) of 592 patients with thyrotoxicosis. This ratio was 41.5% in patients with Graves' thyrotoxicosis and 40.7% of them had a solitary nodule. Similarly, thyroid nodules were determined in 27 (30.6%) of 88 subjects with thyroiditis and 22 (29.3%) of 75 subjects with gestational thyrotoxicosis. The number of thyroid nodules were higher in patients with TMNG in comparison with patients with TA (p<0.001), GD (p<0.001), thyroiditis (p<0.001), and gestational thyroiditis (p<0.001), as expected. The mean nodule size was larger in patients with TMNG in compared to patients with GD (p<0.001), thyroiditis (p<0.001) and gestational thyroiditis (p<0.001). Patients with TA also had higher size of nodules than those with GD (p<0.001), thyroiditis (p<0.001) and gestational thyrotoxicosis (p<0.001) (Table 3).

Discussion

Our results indicate that TMNG is the most common cause of thyrotoxicosis in our population and the clinical presentation of patients vary according to the underlying cause.

Thyrotoxicosis is a condition having multiple etiologies and manifestations. In the United States, the prevalence of hyperthyroidism is approximately 1.2% and GD is overall the most frequent clinical form of thyrotoxicosis (5,6). In New Zealand, GD is the main cause of thyrotoxicosis (64%) and this ratio is 27% for TMNG (1). Reinwein et al. observed similar ratios for GD (59.6%) and toxic nodular goiter (9.2%) in six countries of Europe (2). GD is the most frequent cause also in Canada (70%) (3). Recently, a study from Pakistan showed that the most common form of thyrotoxicosis was GD (53%) followed by TMNG (20.1%) (10).

Our data show a greater percentage of TMNG than the data of these authors. Lundgren et al. found similar ratios with our findings in Sweden where goiter has been considered endemic (11). The prevalence of toxic nodular goiter increases in the presence of iodine deficiency (7). Turkey is a region of endemic goiter and iodine deficiency is the primary etiological factor. For this reason, mandatory iodization of household salt was started in 1999 (12). Rize city is known to be an iodine-deficient area with 14 mg/L urinary iodine concentrations (12,13). Therefore, TMNG is more common than GD in our population. As iodized salt has began to be used 14 years ago, GD is the leading cause among young, whereas TMNG in the elderly. Since the problem of iodine deficiency had been solved in Turkey for more than a decade now, the incidence of toxic nodular goiter may fall in

Table 3. Biochemical and ultrasonographic features of the patients

Parameter	Graves' disease n=130	Toxic adenoma n=57	Toxic multinodular goiter n=242	Thyroiditis n=88	Gestational thyrotoxicosis n=75	p
Severity of thyrotoxicosis Subclinical (%) Mild (%) Moderate (%) Severe (%)	26.1% (34) 23% (30) 27% (35) 23.9% (31)	54.4% (31) 38.8% (22) 5.1% (3) 1.7% (1)	58.7% (142) 34.7% (84) 5.8% (14) 0.8% (2)	50% (44) 40.9% (36) 9.1% (8) 0%	50.7% (38) 48% (36) 1.3% (1) 0%	<0.001**
FT3 (N:1.71-3.71 pg/mL)	8.60±0.70	4.15±0.26	3.82±0.11	3.91±0.14	3.86±0.10	<0.001*
FT4 (N:0.7-1.48 ng/dL)	2.58±0.54	1.38±0.05	1.40±0.02	1.56±0.02	1.51±0.05	<0.001*
TSH (N:0.35-4.94 uIU/mL)	0.04±0.007	0.10±0.01	0.10±0.006	0.09±0.01	0.08±0.01	<0.001*
TGAb (N:0-4.11 uIU/mL)	190.31±27.11	14.7±10.64	44.57±10.42	144.59±28.43	22.12±6.84	<0.001*
Presence of TGAb (%)	65.3% (85)	14.8% (8)	26.4% (59)	58.6% (51)	30.5% (22)	<0.001**
TPOAb (N:0-5.61 uIU/mL)	264.09±44.16	14.01±6.82	22.97±7.08	105.45±27.15	6.70±3.23	<0.001*
Presence of TPOAb (%)	63% (82)	11.1% (6)	17.1% (38)	29.8% (26)	12.5% (9)	<0.001**
Number of nodules	1.83±0.13	1.07±0.03	3.49±0.09	2.19±0.28	1.91±0.35	<0.001*
Nodule size (mm)	13.05±0.90	30.37±2.20	27.45±0.72	14.84± 2.0	11.73±1.19	<0.001*

Values are expressed as means ± SEM
*Kruskal Wallis **Chi square test
TGAb: anti-thyroglobulin autoantibody, TPOAb: anti-thyroid peroxidase autoantibody

future (14). Baltisberger et al. observed an impressive reduction in the prevalence of TMNG 15 years after the doubling of the iodine content of salt in Switzerland (15).

The prevalence of toxic nodular goiter increases with age (7). Our data confirm previous findings of an increased prevalence of toxic nodular hyperthyroidism in older patients (2,16). In our study, toxic nodular goiter was more common in older people compared to the other clinical forms of this disorder. 79.4% of patients over 65 years old were diagnosed with TMNG.

The assessment of signs and symptoms of thyrotoxicosis is essential for formulating an appropriate treatment plan. The importance of age as a determinant of the prevalence and severity of hyperthyroid symptoms has been recently confirmed (17). Boelaert et al. examined 3049 patients with hyperthyroidism and demonstrated that more than 50% of patients aged 61 years or older presented with very few symptoms of hyperthyroidism, whereas this proportion was significantly lower (around 30%) in younger patients (17). In another study of 84 patients with overt thyrotoxicosis, atrial fibrillation and anorexia dominated in patients aged ≥70 years, while nervousness, weight loss, palpitations, tremor and heat intolerance were more frequently observed in younger patients (≤50 years) (18). The results of our study are comparable with the data of these authors.

Importantly, our findings indicate the association between clinical manifestation and disease etiology that was not considered in studies of Boelaert and Trivalle et al. (17,18). Probably, advancing age in TMNG and higher elevation of serum fT3 and fFT4 levels in GD create the difference in clinical presentation. Most of the patients with GD had the classical signs of thyrotoxicosis, while the other patients were oligosymtomatic. Weight loss was more frequently observed in patients with GD, while cardiac arrhythmia dominated in patients with TMNG.

Subclinical hyperthyroid disease is more commonly observed in women than in men, in blacks than in whites, in the elderly and in patients with low iodine intake (7,19). The incidental finding of low TSH levels on routine investigation for other indications is the first evidence for toxic nodular disease, particularly in regions of iodine deficiency (20). In our study, subclinical thyrotoxicosis was present in 49% of patients and, 44.5% of them were diagnosed with TMNG. More than half of the patients with TMNG, TA, thyroiditis and gestational thyroiditis presented with subclinical thyrotoxicosis.

GD was the most frequent cause of severe thyrotoxicosis in the current study. 80-100% of untreated patients with thyrotoxicosis caused by GD have detectable TSHR antibodies (21). In our study, this ratio was 58.9%. This may be associated with the sensitivity of the assay. TGAb and TPOAb were present in majority of patients with GD in this study.

Painless thyroiditis is the etiology of hyperthyroidism in about 10% of patients (3). In our study, the frequency of painless thyroiditis was 11.3%. In 6 patients, thyrotoxicosis occured in the postpartum period. In 3 subjects, painless thyroiditis was associated with amiodarone therapy and it was induced by interferon-α therapy in one patient. Thyroid dysfunction caused by thyroiditis was less severe than that seen with GD.

In conclusion, TMNG is the most common cause of thyrotoxicosis in Rize, which is an iodine-deficient area and the clinical presentation and severity of thyrotoxicosis vary according to the underlying cause.

Conflicts of Interest

There are no conflicts of interest.

References

1. Brownlie BE, Wells JE. The epidemiology of thyrotoxicosis in New Zealand: incidence and geographical distribution in north Canterbury, 1983-1985. Clin Endocrinol (Oxf) 1990;33:249-259.
2. Reinwein D, Benker G, König MP, Pinchera A, Schatz H, Schleusener A. The different types of hyperthyroidism in Europe. Results of a prospective survey of 924 patients. J Endocrinol Invest 1988;11:193-200.
3. Williams I, Ankrett VO, Lazarus JH, Volpe R. Aetiology of hyperthyroidism in Canada and Wales. J Epidemiol Community Health 1983;37:245-248.
4. Berglund J, Ericsson UB, Hallengren B. Increased incidence of thyrotoxicosis in Malmö during the years 1988-1990 as compared to the years 1970-1974. Intern Med 1996;239:57-62.
5. Davis PJ, Davis FB. Hyperthyroidism in patients over the age of 60 years. Clinical features in 85 patients. Medicine (Baltimore) 1974;53:161-181.
6. Tibaldi JM, Barzel US, Albin J, Surks M. Thyrotoxicosis in the very old. Am J Med 1986;81:619-622.
7. Laurberg P, Pedersen KM, Vestergaard H, Sigurdsson G. High incidence of multinodular toxic goitre in the elderly population in a low iodine intake area vs. high incidence of Graves' disease in the young in a high iodine intake area: comparative surveys of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. J Intern Med 1991;229:415-420.
8. Reid JR, Wheeler SF. Hyperthyroidism: diagnosis and treatment. Am Fam Physician 2005;72:623-630.
9. Marqusee E, Haden ST, Utiger RD. Subclinical thyrotoxicosis. Endocrinol Metab Clin North Am 1998;27:37-49.
10. Ahsan T, Banu Z, Jabeen R, Farooq MU. Clinical spectrum and various forms of thyrotoxcosis in endocrine clinic of Jinnah Postgraduate Medical Centre. J Pak Med Assoc 2013;63:354-357.
11. Lundgren E, Borup Christensen S. Decreasing incidence of thyrotoxicosis in an endemic goitre inland area of Sweden. Clin Endocrinol (Oxf) 1990;33:133-138.
12. Erdoğan G, Erdoğan MF, Delange F, Sav H, Güllü S, Kamel N. Moderate to severe iodine deficiency in three endemic goitre areas from the Black Sea region and the capital of Turkey. Eur J Epidemiol 2000;16:1131-1134.
13. Erdoğan G, Erdogan MF, Emral R, Baştemir M, Sav H, Haznedaroğlu D, Ustündağ M, Köse R, Kamel N, Genç Y. Iodine status and goiter prevalence in Turkey before mandatory iodization. J Endocrinol Invest 2002;25:224-228.
14. Erdoğan MF, Demir O, Emral R, Kamel AN, Erdoğan G. More than a decade of iodine prophylaxis is needed to eradicate goiter among school age children in a moderately iodine-deficient region. Thyroid 2009;19:265-268.
15. Baltisberger BL, Minder CE, Bürgi H. Decrease of incidence of toxic nodular goitre in a region of Switzerland after full correction of mild iodine deficiency. Eur J Endocrinol 1995;132:546-549.
16. Siegel RD, Lee SL. Toxic nodular goiter. Toxic adenoma and toxic multinodular goiter. Endocrinol Metab Clin North Am 1998;27:151-168.
17. Boelaert K, Torlinska B, Holder RL, Franklyn JA. Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. J Clin Endocrinol Metab 2010;95:2715-2726.
18. Trivalle C, Doucet J, Chassagne P, Landrin I, Kadri N, Menard JF, Bercoff E. Differences in the signs and symptoms of hyperthyroidism in older and younger patients. J Am Geriatr Soc 1996;44:50-53.
19. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol (Oxf) 1991;34:77-83.
20. Toft AD. Clinical practice. Subclinical hyperthyroidism. N Engl J Med 2001;345:512-516.
21. Zöphel K, Roggenbuck D, Wunderlich G, Schott M. Continuously increasing sensitivity over three generations of TSH receptor autoantibody assays. Horm Metab Res 2010;42:900-902.