Etiology of Overt or Subclinical Hyperthyroidism and Iodine Status in Older Than Sixty Years

60 Yaş ve Üzeri Hastalarda Aşikar ya da Subklinik Hipertiroidi Etyolojisi ve İyot Durumu

Hipertiroidi, İyot, Yaşlı / Hyperthyroidism, Iodine, Elderly

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Özet

Amaç: Tiroid disfonksiyou yaşlı populasyonda mortalite ve ve morbiditeyle ilgili olarak yaygın olarak görülmektedir. Graves Hastalığı tüm hipertiroidizmin nedenleri arasında en sık görülendir. TMNG ise yaşlı popülasyonda daha sık görülmektedir. Tiroid hormonu sentezi için iyot temel moleküldür. Tiroid bezi içersinde iyota oldukça duyarlı olan otonomi kazanmış alanlar oluşabilir. Çalışmamızda 60 yaş ve üstündeki hastalarda hipertiroidi etiyolojisini araştırmayı planladık. Gereç ve Yöntem: Bu çalışmaya 60 yaş ve üstü aşikar ve subklinik hipertiroidi tanısı olan 100 hasta dahil edildi. Hastaların demografik ve klinik özellikleri kaydedildi. Tüm hastaların Anti-tiroid antikorları, tiroid ultrasonografileri ve tiroid sintigrafik incelemeleri yapıldı. Tüm hastaların 24 saatlik idrarda iyot atılımı incelendi. Bulgular: Çalışmaya katılan 81 hasta (%81) aşikar, geriye kalan 19 hasta (%19) ise subklinik hipertiroidi olarak değerlendirildi, bu hastalarda ortalama yaş 70.48 ± 6.16 (60-88 arası) olarak saptandı. İyot maruziyeti 30 hastada mevcuttu ve 11 hastada ise JBP görüldü. En yaygın hipertiroidi nedeni TMNG (%29.2) idi, 8 hastaya herhangi bir tanı konulamadı ve bu hastalar nondiyagnostik (ND) olarak tanımlandı. Tartışma: Bu çalışma yaşlı popülasyonda tirotoksikozun sebeplerinin araştırıldığı ilk çalışmadır. Sonuçlarımız bu popülasyonda TMNG'nin en sık neden olduğunu göstermiştir. JBP olan hastaların öykülerinde iyot maruziyeti mutlaka vardır. Bu sebeple özellikle radyokontrast madde kullanımı olan yaşlı popülasyonda bu durum dikkatli bir şekilde değerlendirilmelidir.

Anahtar Kelimeler

60 Yaş Üstü; Hipertiroidi; Subklinik Hipertiroidi

Abstract

Aim: Thyroid dysfunction is common among older people associated with morbidity and mortality. Overall, the most common cause of hyperthyroidism is Grave's Disease (GD). In the older population however, Toxic Multinodular Goitre (TMG) is more common. Iodine is an essential molecule for thyroid hormone synthesis. This may be due to the presence of autonomic areas with a higher sensitivity to iodine in the thyroid gland. The aim of this study was to detect the etiology of hyperthyroidism among cases older than 60 years. Material and Method: The study included 100 patients ≥60 years or older with hyperthyroidism. Demographic and clinical features of the patients were recorded. All patients were tested for anti-thyroid autoantibodies and underwent thyroid ultrasonographic (USG) and scintigraphic examination. Iodine exposure was detected in 24-hour urine specimens. Results: Eighty-one patients (81%) had overt and the remaining 19 (19%) had subclinical hyperthyroidism and the mean age was 70.48 ± 6.16 (range 60-88). Thirteen patients had recent exposure to iodine and 11 had Jod Basedow Phenomenon (JBP). The most common disease was TMNG (29.2%) and 8 patients had no definitive diagnosis; they were designated nondiagnostic (ND). Discussion: This is the first study that investigates the causes of thyrotoxicosis amoung older people in our country. The results indicated that TMNG was the most common cause. JBP cases had a history of exposure to iodine. For this reason, radiocontrast use in older people should be carefully evaluated with this respect.

Keywords

Older Than 60 Years; Hyperthyroidism; Subclinical Hyperthyroidism

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Introduction

Hyperthyroidism is the exposure of tissues with increased concentrations of thyroid hormones [1]. Hyperthyroidism is more common among women than in men [2]. The most common symptoms of hyperthyroidism are anxiety, nervousness, weakness, weight loss despite increasing appetite, intolerance to heat, sweating, tremor, palpitation, insomnia, increasing frequency of stools, oligomenorrhea and amenorrhea in women and gynecomastia and erectile dysfunctions among men [3].

The most common three causes of hyperthyroidism are Graves Disease (GD), Toxic Multinodular Goiter (TMNG) and Toxic Nodular Goiter (TNG). Graves Disease accounts for 60-90% of all hyperthyroidism cases [4]. However, the frequency of TMNG increases among older cases. Somatic mutations were detected in the thyroid stimulating hormone (TSH) receptor gene in 20-80% of patients [5-6]. Excessive iodine may cause hyperthyroidism in individuals who live in endemic goiter regions or in the presence of autonomic nodules in the thyroid gland; this is called Jod Basedow Phenomenon (JBP) [7]. Iodine exposure may be detected by examining 24-hour urine samples in such patients [8].

The definitive diagnosis of hyperthyroidism in the aged population is important because it is a major cause of morbidity and mortality. The classic symptoms of thyroid dysfunction are usually absent or may be overlooked in older patients, making the diagnosis and subsequent management challenging. However, there is no study on the etiology of hyperthyroidism among the older population in Turkish population. In this study, we aimed to determine the etiology of hyperthyroidism among individuals ≥60 years.

Material and Method

Patient selection: Thyroid function tests (TFT) were done in individuals ≥60 years. The study group included 100 patients with hyperthyroidism with high levels of sT3 and sT4 and low levels of TSH and subclinical hyperthyroidism cases with normal levels of sT3 and sT4 and TSH levels <0.10. Gender, age, history and symptoms-sweating, tremor, nervousness, palpitation, weight loss, insomnia-were recorded.

Laboratory tests: Laboratory tests included fasting glucose (FG), creatinine (Cre), alanin aminotranspherase (ALT), hemoglobin (Hb), white blood cells (WBC), plateletes (Plt), ATPO, ATG, and TRAb (Serum samples were centrifuged at 3000 rpm for 10 minutes and radioimmunoassay technique was utilized using the Brahms kits. Normal range for TRAbs was considered 0-10 u/l; levels over 10 u/l were considered positive) as well as thyroid function tests (TFT). Iodine level in 24-hour urine samples was detected by Sandell-Kolthoff method spectrophotometrically. The results were categorized as severe deficiency for <20 µg/l, intermediate deficiency for 20-50 µg/l, mild deficiency for 50-100 µg/l, normal iodine intake for 100-200 µg/l, higher than normal iodine intake for 200-300 µg/l and excessive iodine intake for >300 µg/l. All patients underwent thyroid ultrasonographic examination and scintingraphy. Thyroid USG examined the size and the parenchymal structure of the thyroid gland and the presence of nodules. Thyroid scintigraphy revealed the shape and the contours of the thyroid gland and the uptake of technetium by the gland.

Statistical analysis:Statistical analysis was run by SPSS version 15.0. Continuous variables were expressed as arithmetic mean ± standard deviation, categorical variables were expressed as percentages. Continuous variables were compared with One-way ANOVA and chi-square test was used for categorical variables. A p value <0.05 was considered statistically significant.

Results

This study included 100 patients with overt hyperthyroidism or subclinical hyperthyroidism with TSH levels < 0.1. Of the patients, 43 were male and 57 were female. Eighty-one patients (81%) had overt and the remaining 19 (19%) had subclinical hyperthyroidism and the mean age was 70.48 ± 6.16 (range 60-88). Thirteen patients had recent exposure to iodine. The mean levels of various biochemical parameters were T3 4.33 ± 2.91 ng/dL, sT4 1.80 ± 1.03 ng/dL, TSH 0.04 ± 0.10 µ/mL, cre 1.09 ± 1.02 mg/dl, FG 119.12 ± 57.29 mg/dl, ALT 22.08 ± 12.75 u/l, WBC 7,27 ± 2.32 103/µL, HB 13.3 mg/dl, PLT 238 x103/µL. The mean amount of iodine in 24-hour urine samples was 200.62 ± 138.30 µg/day (Table-1)

Table 1. Laboratory values of all patients Laboratory values of all patients

Gender (M/F)	43/57
Age (Years)	70.48 ± 6.16 (60-88)
White Blood Cell (103/Ml)	7.27 ± 2.32 (1.28-1.41)
Creatinine (mg/dL)	1.09 ± 1.02 (0.5-8.3)
Alanine Transaminase (U/L)	22.08 ± 12.75 (22-76)
Free T3 ((ng/dL)	4.33 ± 2.91 (1.79-22)
Free T4 ((ng/dL)	1.80 ± 1.03 (0.6-6)
TSH (µlU/mL)	0.04 ± 0.10 (0-0.9)
Urine iodine amount (µg/day)	200.6 ± 138.3 (26-750)

Data were expressed as mean ± Standard error.

The most common condition was TMNG. Patients were categorized in five groups. The first group TMNG included 29, the second group GD included 25, the third group TNG 24, and the fourth group JBF 14 patients. The remaining 8 patients were included in the fifth group designated Nondiagnostic (ND). The overall results were shown in (Table 2).

Table 2. Etiology of the hyperthyroidism in the study group

Etiology	N (%)
Toxic Multinodular Goiter	29
Grave's Disease	25
Toxic Nodular Goiter	24
Jod Basedow Phenomenon	14
Non-diagnostic	8

The most common symptom was intolerance to heat in 79 patients. The clinical features of the patients according to causes of hyperthyroidism were shown in (Table 3). Comparison of laboratory parameters among patient groups did not reveal any significance for FG, Cre, ALT, WBC, Plt, Hb, sT3, sT4 and TSH. Grave's disease was diagnosed in 7 out of 10 patients with ATPO antibodies, in 9 patients out of 12 with ATG antibodies and all 6 patients with TRAb antibodies. Grave's disease was correlated with ATPO (p<0.01), ATG (p<0.001) and TRAb (p<0.001) (Table 4). Jod Basedow Phenomenon was pres-

Table 3. Clinical features of the patients with hyperthyroidism according to etiology

Features (Present/absent)	TMNG n=29	GD n=25	TNG n=24	JBP n=14	ND n=8
Symtoms	26/3	24/1	19/5	2/12	5/3
Sweating	21/8	21/4	18/6	10/4	5/3
Palpitation	18/11	16/9	10/14	6/8	2/6
Weight loss	8/21	6/19	4/20	3/11	0/8
Insomnia	5/24	5/20	4/20	1/13	0/8
Tremor	7/22	9/16	5/19	1/13	1/7
Intolerance to heat	25/4	22/3	17/7	10/4	5/3
Nervousness	4/24	9/16	3/21	3/11	0/8
Fever	0/29	1/24	0/24	0/14	0/8
Visual problems	0/29	0/29	0/24	0/14	0/8
Ophtalmopathy	0/29	5/20	0/24	0/14	0/8

Table 4. Comparisons of the laboratory parameters

	TMNG n=29	GD n=25	TNG n=24	JBP n=14	ND n=8
Age	70.2±4.8	68.5±7.3	73±5.6	68±5.8	74±5.3
Gender (M/F)	9/20	11/14	13/11	7/7	3/5
Creatinine (mg/dL)	1.2±1.7	0.9±0.5	0.93±0.1	1.25±0.8	1.17±0.2
ALT (U/L)	20.1±13	23.8±13.5	20.7±10.5	23.1±14.1	25.7±14.1
FreeT3 (ng/dL)	4.7±2.4	5.2±4.8	4±1.04	3.1±1.3	3.08±0.7
Free T4 (ng/dL)	1.7±0.9	2.2±1.2	1.5±1	1.8±0.8	1.3±0.3
TSH(µI/mL)	0.03±0.06	0.02±0.04	0.03±0.05	0.07±0.05	0.14±0.3
AntiTPO (+/-)	2/27	7/18	0/24	1/13	0/8
AntiTG (+/-)	0/29	9/16	1/23	2/12	0/8
TRAb (+/-)	0/29	6/19	0/24	0/14	0/8
Subclinical hyperthyroidism	5/29	3/25	8/24	2/14	1/8
Overt hyperthyroidism	24/29	22/25	16/24	12/14	7/8
WBC (103/µL)	7.04±2.1	7.02±2.2	7.18±1.9	8.65±3.1	6.81±1.9

TMNG, Toxic Multinodular Goiter; GD, Grave's Disease; TNG, Toxic Nodular Goiter; JBF, Jod Basedow Phenomenon; ND, Nondiagnostic, ALT, Alanine Transaminase FT3, free triiodothyronine FT4 free tetraiodothyronine; TSH; Thyroid Stimulating hormone, WBC, White Blood Cell; AntiTPO, Anti Thyroid Peroxidase antibody; AntiTG Antithyrogloguline Antibody TRAb TSH receptor antibody

ent in 11 out of 13 patients with iodine exposure. Jod Basedow Phenomenon significantly correlated with iodine exposure (p<0.001). The mean amount of iodine in 24-hour urine samples was 172.86 ± 129.77 TMNG, 171.24 ± 103.54 for GD, 159.95 ± 93.42 for TNG, 382.71 ± 16.01 for JBP and 196.37 ± 103.45 for ND. JBP significantly correlated with the amount of iodine in urine (p<0.001) (Table-5).

Discussion

Thyroid dysfunction is a common condition in old age with significant morbidity and mortality [9-10]. The classical symptoms of hyperthyroidism are vague in older patients. Such patients usually present with cardiopulmonary symptoms and complications such as tachycardia, AF, respiratory distress and cardiac failure [11]. Thus, thyrotoxicosis should be diagnosed early and accurately and treated appropriately to prevent complications.

It is well-established that GD is the most common cause of hyperthyroidism [4-12]. On the other hand, TMNG is more common among elderly. However, there is no other study investigating the causes of thyrotoxicosis among older individuals. In a study from Turkey including 116 patients with thyroid dysfunction, where almost half of the patients (50/116) were over 65 years, diagnosis was overt hypothyroidism in 0.4%, subclinical hypothyroidism in 8.5%, subclinical hyperthyroidism in 30%, and overt hyperthyroidism in 16%. However, the study did not investigate the causes of hyperthyroidism [13]. In a report from Denmark including 2 027 208 patients, 1682 were diagnosed with overt hyperthyroidism. All patients underwent thyroid scintigraphy and were investigated for thyroid autoantibodies [14]. The results revealed that 44.1% of patients had TMNG, 37.6% GD, 5.7% TNG, 5.4% mixed type (TRAb positive, scintigraphic multinodular), 2.3% subacute thyroiditis, 2.2% postpartum thyroiditis, 0.8% amiodarone-associated hyperthyroidism and 0.7% lithium-associated hyperthyroidism. Although the coverage rate was high in the study, 24-hour urine samples were not tested for iodine. Thus, JBP diagnosis might have been missed in middle- and old-aged patients who live in endemic goitre regions. In addition, the study included patients with overt hyperthyroidism with high sT3 and sT4 levels and low TSH levels. However, in elderly patients, systemic diseases or stress that decreases serum T3 levels may inhibit the T3 response to hyperthyroidism. Thus, the exclusion of subclinical hyperthyroidism patients from the study could have influenced the results of the study.

In our study, 24-hour urine samples were tested for iodine levels in all patients. Iodine is an essential molecule for thyroid hormone synthesis. The dietary amount of iodine should be 150 µg/day. Only 20% of the iodine ingested with food is taken by the thyroid gland and the rest is excreted with urine. The mean level of iodine in our study was 200.62 ± 138.30 µg/day. This suggests excessive dietary iodine intake in our country where the major source is likely to be salt. Another important finding

Table 5. Iodine status of the patients

		TMNG n=29	GD n=25	TNG n=24	JBP n=14	ND n=8
Iodine exposure (n)		0	1	1	11	0
Urine iodine (µg/day)		172.8±129.7	171.2±103.5	159.9±93.4	382.7±162	196.3±103.4
		7		4	2	4
Urine iodine	<150	19	13	15	1	
	150-200	3	6	3	6	
	200-300	3	3	3	4	
	>300	4	3	3	10	1

of the study was the high number (14 cases) of JBP cases where 11 had a history of exposure to radiocontrast substance. Radiocontrast use in older people should be carefully evaluated with this respect. The high number of JBP, TMNG and TNG patients is parallel to the results of a study from Denmark. This may be due to the presence of autonomic areas with a higher sensitivity to iodine in the thyroid gland of our study patients who spent their childhood and early adulthood in Isparta-where the study was run-which is an endemic goiter region.

Blood samples were collected from each patient for TRAb test. As mentioned above, there are two TRAbs-stimulator and inhibitor. While stimulator TRAb is specific for GD, inhibitor antibodies may also be present in Hashimato disease, type-1 diabetes, primary biliary cirrhosis, Sjogren's syndrome, autoimmune hepatitis, systemic lupus erythematosus, and myastenia gravis patients [15]. Among 100 patients included in our study, 6 were positive for TRAb; they all had GD. Thus, the false positivity rate for this antibody specific for GD was zero. In addition, TRAb was positive in all five patients with ophtalmopathy. Reports from other countries suggest that TRAb is specific for GD [16]. In addition, they have a major role in the pathogenesis of graves ophthalmopathy and pretibial myxedema [17-18]. From another perspective, TRAb was positive only in 6 out of 25 patients (25%) with GD. Other studies reveal discrepant results with TRAb positivity in more than 90% of GD patients [19-20]. This may be due to the use of different measuring methods and reference ranges. It may also be due to the reduction in serum levels with old age.

While the most common symptom was intolerance to heat, sweating, weight loss, and tremor, 14 patients were asypmtomatic. Similar results were obtained in 2/3 of studies investigating hyperthyroidism symptoms in the elderly population [11-21]. We had mentioned that symptoms such as sweating, intolerance to heat and tremor were milder in older patients due to increasing sympathetic activity and respiratory distress and weight loss would be more common compared to younger patients. However, the high number of asymptomatic patients overlaps with the novel concept of apathetic hyperthyroidism. Thus, we suggest physicians to take a detailed history and test for TSH levels in older patients regardless of the reason for their hospital visit.

Eight patients were undiagnosed in our study. Their mean iodine level was 196.37 ± 103.45 µg/day, ATPO, ATG, and TRAb were negative and they showed medium technetium uptake in the scintigraphic examination. If we could have done the RAIU test in those patients, a much more accurate interpretation of their conditions would have been possible. However, it was not possible to purchase the test due to budget limitations.

In conclusion, this is the first study that investigates the caused of thyrotoxicosis in our country. The results indicated that TMNG was the most common cause. However, the small number of patients was the major limitation of the study. Further large-scale studies including the radioactive iodine uptake test are required.

Competing interests

The authors declare that they have no competing interests.

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