ORIGINAL ARTICLE

EVALUATION OF THYROID DISORDERS IN EFFECTIVELY TREATED ACROMEGALIC PATIENTS

Etkili Tedavi Edilmiş Akromegali Hastalarında Tiroid Bozuklarının Değerlendirilmesi

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ABSTRACT

Objective: Acromegaly patients often develop goiter and thyroid nodules due to continuous stimulation of the thyroid follicle by growth hormon (GH) and insulin-like growth factor-1 (IGF-1). Recent studies suggest a decrease in thyroid disease rates in patients who have been successfully treated. This study aimed to investigate thyroid disorders in patients who had cured or controlled the disease.

Material and Methods: The patients who were surgically cured or were controlled with at least six months of somatostatin treatment were included in the study. The patients' GH levels were less than 1 ng/mL, and IGF-1 levels within the age sex adjusted normal range were categorized into controlled patients. Sonographic and biochemical findings of the thyroid gland were recorded.

Results: The study included 33 patients with acromegaly (14 males and 19 females) and 50 volunteers (14 males and 36 females). The prevalence of goiter was higher in patients with acromegaly compared to control group (21.2% vs. 6%, respectively; p<0.001). Acromegaly patients had a higher frequency of thyroid nodules, but nodules larger than 1 cm were similar between the two groups.

Conclusion: Acromegaly patients still have a high multinodular goiter incidence. Well control of disease may reduce the prevelance of thyroid cancer and risky nodules.

Keywords: *Acromegaly; Thyroid Disease; Thyroid Nodule*

ÖZET

Amaç: Tiroid foliküllerinin growth hormon (GH) ve insülin-like growth faktör-1 (IGF-1) aracılığıyla sürekli uyarılması akromegali hastalarında guatr ve tiroid nodüllerinin gelişmesine neden olur. Güncel çalışmalar, başarılı şekilde tedavi edilen hastalarda tiroid hastalığı sıklığının azaldığını ileri sürmektedir. Bu çalışma, kür veya kontrol altına alınmış hastalardaki tiroid bozukluklarını araştırmak için yapılmıştır.

Gereç ve Yöntemler: Cerrahi olarak kür sağlanan veya en az 6 ay somotostatin tedavisi verilerek kontrol altına alınmış hastalar çalışmaya dahil edildi. GH düzeyleri 1ng/mL'den düşük ve IGF-1 seviyeleri yaşa ve cinsiyete göre normal aralıkta olan hastalar kontrol altına alınmış hastalar olarak kategorize edildi. Tiroid bezinin sonografik ve biyokimyasal bulguları kaydedildi.

Bulgular: Çalışmada 33 akromegali hastası (14 erkek ve 19 kadın) ve 50 gönüllü yer aldı. (14 erkekve 36 kadın). Akromegali hastalarındaki guatr sıklığı kontrol grubuna kıyasla daha fazla idi (sırasıyla, %21,2 ve %6, p<0,001). Akromegali hastalarında tiroid nodülü daha sık görülmekle beraber 1 cm'den büyük nodül sıklığı iki grup arasında benzerdi.

Sonuç: Akromegali hastalarında multinodüler guatr sıklığı halen yüksektir. Hastalığın tam kontrol altına alınması tiroid kanseri ve riskli nodül sıklığını azaltabilir.

Anahtar Kelimeler: *Akromegali; Tiroid Hastalıkları; Tiroid Nodülü*

INTRODUCTION

Acromegaly is a rare disease caused by excessive secretion of growth hormone (GH), typically caused by a pituitary adenoma (1). The prevalence of acromegaly is approximately 2.8–3.7/100000 (2). A high GH level induces the liver to produce excess insulin-like growth factor-1 (IGF-1), leading to characteristic clinical manifestations. The slow progression of symp-toms and signs often causes diagnostic delays. Long-term exposure to high IGF-1 levels may result in hypertension, cardiomyopathy, diabetes, and obstructive sleep apnea (3).

The thyroid gland is the most affected organ in patients with acromegaly. Although the majo-rity of patients have normal thyroid function, goiters and thyroid nodules frequently develop as a result of GH and IGF-1 stimulation of the thyroid follicle (2). In some studies, the positi-ve correlation between IGF-1 levels, thyroid volume (TV), and thyroid nodules has been de-monstrated (4,5).

Thyroid cancer is the most common malignancy in acromegalic patients, but it is controversial whether acromegaly is an independent risk factor for thyroid cancer. In contrast to earlier research, recent studies suggest that the rate of thyroid cancer in controlled acromegaly pati-ents has not risen in comparison to the general population. This is still a matter of debate (6). There is insufficient data on changes in the thyroid gland in patients who were successfully treated. We conducted this study to examine the condition of thyroid disease in patients with cured or controlled disease.

MATERIAL AND METHODS

We conducted a cross-sectional study on following-up acromegaly patients at Saglik Bakanligi Istanbul Medeniyet University Goztepe Training and Research Hospital. The local ethics committee accepted the study protocol (no:20150127, date:10.12.2015). The study included 33 patients who were surgically cured or were controlled with at least six months of somatostatin treatment. Four active acromegaly patients were excluded. Fifty healthy volunteers were included as a control group. The criteria for surgical cure are defined as having an age-adjusted IGF-1 level within the normal range and a random GH level below 1 ng/mL, or a nadir GH level below 0.4 ng/mL on an oral glucose tolerance test. The controlled patient was defined as having GH levels less than 1 ng/mL and IGF-1 levels were not within the age-sex adjusted normal range. Patients with abnormal GH and IGF-1 levels were accepted as having an active disease (3).

The thyroid was examined using high-resolution B-mode ultrasound images obtained with a 7.5 Hz linear array transducer (EUB 7000 HV; Hitachi, Tokyo, Japan) in all individuals. The ellipsoid model formula (length × thickness × width × 0.52) was used to compute the volume of each tyhroid lobe (7). A goiter was defined as having a total TV greater than 18 mL in ma-les and greater than 13 mL in females. The levels of serum GH, IGF-1, free T4 (fT4), T4, free T3 (fT3), thyroid stimulating hormone (TSH) , anti-thyroid peroxidase (anti-TPO), and anti-thyroglobuline (anti-TG) were measured using chemiluminescent immunometric assays. (Siemens Healthcare, UK). All the nodules detected were measured, and their ultrasound characteristics were registered; cervical lymph nodes were also evaluated. Fine-needle aspiration (FNA) cytology was done on all nodules bigger than 1 cm in diameter and on those between 0.5 and 1 cm in diameter if they had ultrasound features that raised concerns, according to the American Society of Ultrasonography, such as microcalcifications, irregular borders, increased central flow on doppler examination, being taller than wide diameter, hypoechogenicity, and no halo (8). The patients' age at the time of diagnosis and follow-up periods were recorded in the hospital registry system. All the individuals included in the study were briefed about the study, and their informed written consent was obtained.

Statistical Analysis

Categorical variables are presented as a number (percentage). Quantitative data are presented as the mean (± standard deviation). For comparison of categorical variables, use the Chi-squared Test or the Fisher’s Exact Test. The data were tested for normality us¬ing the Shapiro-Wilk and Kolmogorov-Smirnov tests. Student’s t-test was used for normally distributed nu-meric variables, and the Mann-Whitney U-Test was used for non-normally distributed data. Correlation analysis was studied using Spearman's rho test. The

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p<0.05 value was considered statistically significant.

RESULTS

The study included 33 patients with acromegaly (14 males and 19 females, mean age 53 ± 10 years) and 50 volunteers (14 males and 36 females, mean age 50 ± 15 years). The acromegaly patients were diagnosed at 48.4 ± 9.2 years of age. All of them had transsphenoidal surgery for macroadenoma. Seventeen patients were cured by surgery. Twelve patients were control-led with long acting somatostatin analogues, and their treatment was completed. Four patients are still under somatostatin treatment. The duration of treatment was 4.6 ± 1.8 years. The characteristics of patients and volunteers are given in Table 1.

In the acromegaly group, two patients had a history of hypothyroidism. One patient was undergoing iodine restriction treatment for subclinical hyperthyroidism. In the control group, three patients had subclinical hypothyroidism. There was no difference in TSH and fT4 levels between the two groups. Anti-TPO positivity was found in 33% of acromegaly patients and 26% of the control group (p = 0.47). The sonographic and biochemical features of the thyroid gland are presented in Table 2.

Acromegaly patients had a higher TV than the control group (14.73±7.41 mL vs. 11.13±4.33 mL, P = 0.039). Males with acromegaly had a slightly larger TV than females (P = 0.136). The prevalence of goiter was increased in patients compared to controls (21.2% vs. 6%, respectively; p<0.001). Thyroid nodule incidence was 42.4% in patients with acromegaly com-pared to 24.0% in the control group (p<0.001). Multinodular goiter was significantly more frequent in acromegalic patients (p<0.001) (Figure 1). Nodules larger than 1 cm were found in five volunteers and four acromegaly patients. All of them underwent a fine needle aspiration biopsy. One of the patients with acromegaly had a undermined nodule (Bethesta category 3). She underwent another fine needle aspiration biopsy.

Table 1. Characteristics of patients and volunteers

	Acromegaly (n=33)	Control (n=50)	P value
Age (years)	53±10	50±15	0.325
Gender, (male/female)	14/19	14/36	0.178
Age at diagnosis (years)	48.4±9.2	-	-
Treatment duration (years)	4.6±1.8	-	-
BMI (kg/m²)	28.6	25.9	0.156
Random GH level (ng/mL)	0.85 ± 1.3	-	-
Random IGF-1 level (ng/mL)	256.8 ± 127.9	-	-

Data were presented mean±SD
BMI: Body mass index, GH: Growth hormone, IGF-1: Insuline like growth factor-1, kg:kilogram, m²: square meter, ng: nanogram, mL: mililiter

Table 2. Sonographic and biochemical findings of thyroid gland

	Acromegaly (n=33)	Control (n=50)	P value
Thyroid volume (mL) (mean±SD)	14.73±7.41	11.13±4.33	0.039**
Thyroid nodules % (male/female)	42.4% (18.2%/24.2%)	24.0% (6.0%/18.0%)	<0.001***
Single	12.1%	16.0%	0.156
Multiple	27.2%	8.0%	<0.001
Nodule diameter >1cm	12.1%	10.0%	0.189**
TSH (IU/mL)	1.47±2.6	2.9±3.2	0.061**
Free T4 (pg/mL)	1.29±0.6	1.54±1.62	0.072**
Anti-TPO IU/mL	41.3±15.7	36.7±7.2	0.128**
Anti-TG IU/mL	32.3±9.5	29.3±15.7	0.223**

**Fisher's exact test. ***Mann Whitney U test. TSH: Thyroid stimulating hormone, Free T4: Free thyroxine, Anti-TPO: Anti-thyroid peroxidase, Anti-TG: Anti thyroglobuline, mL: mililiter, SD: standard deviation, IU: international unit, mL: mililiter, pg: picogram

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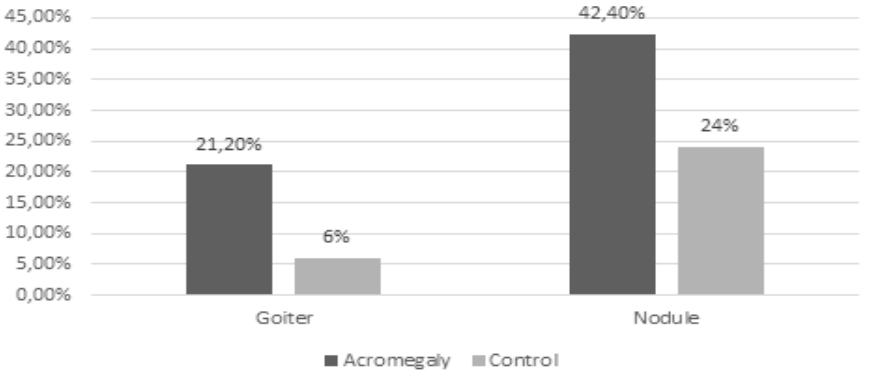

Figure 1. Prevalence of goiter and nodules in patients with acromegaly and controls.

The second biopsy result was Bethesta category 3. The patient was taken under clinical follow-up after obtaining her approval. The other nodules were benign. None of the nodules smaller than 1 cm showed ultrasonic proper-ties that raise suspicion of malignancy.

DISCUSSION

In this study, we assessed 33 controlled acromegaly patients to evaluate thyroid disorders. We found that thyroid dysfunction was present at the same frequency as in volunteers. TV in ac-romegaly was higher than in volunteers. Acromegaly patients had more thyroid nodules, while the number of nodules greater than 1 cm was similar.

Acromegaly can directly and indirectly disrupt the hypothalamic-pituitary-thyroid axis. Thy-roid hormones are usually normal in acromegaly patients, while hypothyroidism and hy-perthyroidism might be present in a small percentage (9). Manavela et al. found that 2.3% of the patients had hypothyroidism and 3.5% had hyperthyroidism. The prevalence of thyroid autoimmunity was 25% in acromegalic patients, whereas in the control group it was 10%. They proposed that thyroid autoimmunity may be a factor in thyroid dysfunction in addition to elevated IGF-1 levels (10). In our study, hypothyroidism was present in 6% and hypertyro-idism in 3% of acromegaly patients. There were no differences between patients and controls in terms of thyroid autoimmunity.

TSH is an essential hormone for thyroid gland growth. Thyrocyte sensitivity to TSH may be increased by growth hormone and IGF-1. Animal studies have revealed that the thyroid follu-cules contain IGF-1 receptors, and IGF-1 stimulation promotes thyroid growth (11). It has been shown in many studies that prolonged exposure of thyroid follicles to high GH and IGF-1 levels can cause goiter and thyroid nodules. Expansion of the thyroid gland can manifest as either diffuse or multinodular (4,12,13).

In a multicenter Italian study involving 258 active acromegaly patients, TV was higher than the control group (23.5±16.9 ml vs. 13.9±12.8 ml, $p<0.001$) (14). Cankurtaran et al. found multinodular goiter (47.3%) and diffuse goiter (14.7%) in 123 acromegalic patients (15). In our study, 9 patients (27.4%) had multinodular goiter, and 2 patients (2%) had diffuse goiter. A study of 34 newly diagnosed patients with active acromegaly followed for 7.3 ± 4.1 years showed a reduction of 19.5 ± 8.1% in thyroid volume with somatostatine treatment. The reason we found a lower prevalence of goiter may be the inclusion of patients with cure or controlled acromegaly.

According to a meta-analysis, the incidence of thyroid nodular disease is higher in acromegaly patients (mixed prevalence = 59.2%, odds ratio [OR] = 6.9, risk ratio = 2.1) than in controls (16). In studies conducted in our country, thyroid nodules were found in approximately 70% of cases. (17,18). We found that the frequency of thyroid nodules was 42.4% in controlled acromegalic patients.

Control of the disease can reduce the number or size of thyroid nodules. In a study, nodule growth increased 1.01 folds for every unit rise in IGF-1 levels, and active acromegaly disease raised nodule growth ninefold (19). Xu et al. found that patients with acromegaly had more

thyroid nodules than patients with a nonfunctioning pituitary adenoma. Furthermore, they demonstrated that the number of vascular and heterogeneous nodules was reduced in patients with post-treatment cure (20). After 12 years of following 92 acromegalies, Doğan et al. observed that the thyroid nodular rate reduced from 69.5 % to 47.8 % with therapy. Patients with nodules had a longer disease duration (14.2 ± 6.6 years) compared to those wit-hout nodules (9.4 ± 3.4 years, p = 0.043) (20). Kan et al. indicated that TV and total thyroid nodule volume are significantly reduced in well-controlled patients. In our study, we found that the frequency of nodules and the number of nodules greater than 1 cm are similar compared to controlled acromegaly patients and volunteers (21).

Cardiovascular and respiratory complications increase mortality and morbidity. Additionally, cancer may raise mortality rates. Prior studies demonstrated that acromegaly increases the risk of colon and thyroid cancer. Gullu et al. identified malignant disease in 15% of 105 patients with acromegaly in a study designed to screen for malignancy. They discovered that thyroid cancer is the most frequently encountered malignancy (22). A meta-analysis of 22 studies published in 2014 revealed that acromegalic patients have a higher incidence of thyroid can-cer, with an odds ratio (OR) of 7.5 and a relative risk (RR) of 7.2. The prevalence of thyroid cancer in this population was found to be 4.3% (23).

Numerous studies have revealed that thyroid cancer prevalence in patients with acromegaly is not significantly different or only slightly increased compared with that observed in the gene-ral population. Some studies have shown that people with acromegaly have a slightly greater risk of thyroid cancer compared to the general population. It's unclear whether there is a hig-her risk of thyroid cancer (6). In another study involving 313 patients conducted in our co-untry, the incidence of thyroid cancer was reported at 6% (24). On the other hand, a retrospective cohort study conducted in Turkey with 129 patients and 247 controls found no statistically significant disparity in the occurrence of thyroid cancer between the two groups (15).

A study conducted on the German Acromegaly Registry revealed that there was no significant increase in the occurrence of thyroid cancer among individuals with acromegaly compared to the general population (25). A Brazil study of 106 patients with acromegaly demonstrated that thyroid cancer occurred in only four patients (3.8%) (26). It may be thought that there is no significant difference in the frequency of thyroid cancer in acromegaly patients due to geographical or racial reasons. In previous studies, the relatively high frequency of TC in acromegaly patients may be due to the fact that the active and controlled patients were not evaluated separately.

In our study, there was no patient with thyroid cancer. Three patients are under follow-up due to an atypia of undetermined significance in a thyroid nodule. In controlled patients, goiter and thyroid nodules are still higher than in the control group. The decrease in thyroid volume and nodule diameter suggests that the thyroid disorders in acromegalic patients may be similar to those in normal populations in the long term. Prospective cohort studies with a large patient population are needed to reveal long-term changes in the thyroid gland and possible risk re-ductions.

CONCLUSION

The effective treatment of patients with acromegaly may reduce thyroid volume, nodule size and volume, and the risk of thyroid cancer. Thyroid volume and nodules can differ dramati-cally with regard to the activity of the disease. Thyroid disorders in acromegalic patients have reached levels that may not matter when the disease is well controlled.

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