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Thyroid diseases in patients with active endogenous Cushing's syndrome

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ABSTRACT

Objective: Data about the impact of Cushing's syndrome (CS) on thyroid is scarce. We aimed to identify the prevalence of thyroid diseases in patients with CS.

Patients and Methods: Nineteen patients with CS and 40 healthy participants were included in the study. All patients were tested for free tri-iodothyronine (fT3), free thyroxine (fT4), thyroid-stimulating hormone (TSH), anti-thyroglobulin (anti-Tg), and anti-thyroid peroxidase (anti-TPO) levels, and thyroid ultrasonography (US).

Results: Overt hypothyroidism, subclinical hypothyroidism, and subclinical hyperthyroidism was evident in 5.3%, 5.3%, and 21.1% of patients with CS; and 2.5%, 7.5%, and 15% of healthy subjects, respectively. fT3 and fT4 levels were lower in patients with CS. None of the patients with CS and 27.5% of the control group had autoimmune thyroid disease (AITD), which was demonstrated by both US findings and anti-TPO positivity (P=0.01). Frequency of thyroid nodule was 52.6% and 52.5% in patients with CS and controls, respectively (P=0.99).

Conclusion: The prevalence of thyroid dysfunction, nodular thyroid disease, and goiter is comparable to healthy population. However, AITD is less prevalent among patients with CS. Although, hypercortisolism has an impact on hypothalamic-hypophyseal-thyroid axis, its clinical implication does not seem to be significant.

Keywords: Cushing's syndrome, Thyroid diseases, Thyroid nodule, Hypercortisolism, Autoimmune thyroid disease

1. INTRODUCTION

Adrenal glucocorticoids can influence hypothalamic-hypophyseal-thyroid axis at several steps including prothyrotropin-releasing hormone (pro-TRH) mRNA, thyrotropin-releasing hormone, thyroid-stimulating hormone (TSH) and TSH-beta mRNA, 5'-monodeiodination of T3 to T4, and T4 to reverse-T3 conversion [1-5]. When compared to healthy volunteers, low levels of TSH in hypercortisolism is accompanied by lower circulating levels of triiodothyronine (T3), thyroxine (T4) and free T3 in these individuals. By contrast, free T4 (FT4) has generally been described as normal. [6].

Hypercortisolism induces a state of immunosuppression by diminishing proinflammatory cytokines, interacting with other transcription factors related with T-cell survival. Autoimmune diseases frequently improve during active Cushing's syndrome (CS). There are several case series reporting overt immune dysfunction and exacerbation of autoimmune thyroid diseases (AITD) upon remission [7-10]. Lower frequency of AITD is expected in patients with CS. However, Onal et al., reported that there was not a difference in the frequency of anti-thyroid autoantibody positivity between the patients with endogenous hypercortisolism and the healthy individuals in contrast to previous studies [11].

Previous studies investigating primary thyroid diseases in patients with CS reported that nodular and diffuse goiter is more prevalent in patients with CS [11-14]. However, these studies have certain limitations. Data are scarce in order to draw a definite conclusion regarding to goiter prevalence within this population.

We aimed to investigate the frequency of thyroid dysfunction, AITD, nodular, and diffuse goiter in patients with CS.

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2. PATIENTS and METHODS

Study Design and the Patients

This study was both retrospective and observational case-control study (Figure 1). All subjects were aged ≥18 years in this study. In retrospective part of the study, data about a total of 74 patients with persistent/recurrent or de novo CS were screened from the patients' medical charts and hospital's medical network. Since we planned to perform this study in patients with active CS, prerequisite for the study inclusion was determined to have thyroid tests performed after the diagnosis and before the treatment of CS, including at least free tri-iodothyronine (fT3), free thyroxine (fT4), TSH, anti-thyroglobulin (anti-Tg), and anti-thyroid peroxidase (anti-TPO) levels, and thyroid ultrasonography (US). Only eleven out of 74 patients were eligible for the study inclusion.

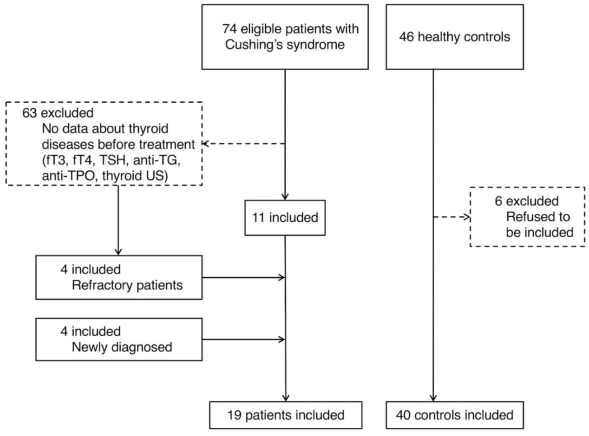

Figure 1. *Study design*

Eight patients, four with newly diagnosed and four with refractory active CS, were recruited for the required study tests. Finally, a total of 19 (17 women and 2 men; median age, 43 [interquartile range: 28 to 54]) patients with CS were included in the study. All patients presented clinical features of CS. Fourteen out of 19 patients had Cushing's disease. Five patients were diagnosed with adrenal adenoma. All patients with refractory disease had Cushing's disease. Median time-to-study testing after the diagnosis was one month (Table 1).

Table I. *Characteristics of the patients with Cushing's syndrome*

Variables	Cushing's syndrome (n=19)	Control (n=40)
Female gender, n (%)	17 (89.5)†	34 (85.0)†
Age, years, median (IQR)	43 (28-54)‡	48 (37-56)‡
Cause of Cushing's syndrome		N/A
Cushing's disease	14 (73.7)	
Microadenoma	12 (85.7)	
Macroadenoma	2 (14.3)	
Adrenal adenoma	5 (26.3)	
Time-to-study testing, months, median (95% CI)	1 (0.78-24.15)	N/A

**NA denotes not applicable; IQR, interquartile range; 95% CI, 95% confidence interval.*

All subjects were informed about the study and a written and signed consent was obtained from each participant. The study was conducted in accordance with the Good Clinical Practice Guidelines [15] according to the principles of declaration of Helsinki and Istanbul University, Cerrahpasa Medical, Surgical and Pharmaceutical Research Ethics Committee approved the study protocol (approval number 2226, date 20.09.2005) [15].

Power and Sample Size Analysis

Power and sample size estimation revealed that at least 40 subjects in control were needed in a 1:2 study design to show a 40% difference with the assumptions that overall type I error of 5%, type II error of 20 percent, number of patients with CS of 20, and frequency of thyroid nodules in CS and healthy people of 60% and 20%, respectively in chi-square test [12]. According to this estimation, at least 17 and 34 patients should be included in the experimental and control arms, respectively.

Controls

Pseudo-Cushing states, including alcoholism, anxiety, depression, poorly controlled diabetes, and morbid obesity; hirsutism, unusual features for the age (e.g., non – traumatic fracture, hypertension, or cutaneous atrophy in young individuals), as well as Cushingoid features and past history of CS were defined as the exclusion criteria for the healthy controls. Pregnant or puerperal women, people who take steroids, antiepileptic drugs, amiodarone, or iodine containing drugs, past history of any severe systemic disease including chronic renal failure were excluded as well.

A total of 46 subjects, who were family members of the patients in Endocrinology clinic, were recruited for the study inclusion. However, later, six withdrew their consents due to lack of their time for the study tests. Finally, 40 (34 women and 6 men; median age, 48 [interquartile range: 37 to 56]) participants were included in the study (Figure 1, Table I).

Definitions

The diagnosis of CS was made by means of several standardized biochemical tests and imaging techniques depending on the availability. A low-dose dexamethasone suppression test, 24-h urinary free cortisol, midnight plasma cortisol, and plasma cortisol circadian rhythm were used to confirm hypercortisolism. The cause of CS was established by additional tests including CRH stimulation, pituitary imaging by magnetic resonance imaging (MRI) with contrast, and bilateral inferior petrosal sinus sampling [16].

The diagnosis of thyroid diseases was made based on commonly accepted clinical and laboratory criteria, including thyroid US, serum TSH and free thyroid hormone levels, anti-TPO antibodies, and anti-Tg receptor antibodies. Overt hyperthyroidism was defined as a TSH< 0.4 mU/L and an FT4 >1.9 pmol/L, and/or a TSH <0.4 mU/L and an fT3 > 4.2 pmol/L; subclinical hyperthyroidism, a normal FT4 and FT3, and a TSH <0.4 mU/L; overt hypothyroidism, a TSH >4.0 mU/L and FT4 <0.8 pmol/L; subclinical hypothyroidism, a normal FT4 and TSH >4.0 mU/L.

Goiter was defined as a thyroid volume exceeding 30.2 mL for males and 20 mL for females. The cut-off levels were extrapolated from the mean (+2 SD) thyroid volume in 251 healthy Turkish subjects (105 males and 146 females) without thyroid dysfunction and/or a previous thyroid disease on ultrasonography [17].

We defined autoimmune thyroid disease (AITD) at two levels: *i.* anti-TPO antibody positivity (anti-TPO$^+$) *ii.* anti-TPO antibody and thyroid US positivity (anti-TPO$^+$/US$^+$) (16). A nonhomogeneous and diffuse hypoechogenic pattern has been accepted as the determinant of AITD on thyroid US [18].

Thyroid nodule was defined as discrete lesions within the thyroid gland which were discriminated from hypoechoic areas by darker appearance in comparison to the surrounding thyroid tissue [19]. Presence of at least one nodule sizing at least two to three mm were defined as nodular thyroid disease.

Measurements

Serum fT3, fT4, and TSH measurements were performed by competitive analog-based immunoassay; solid phase chemiluminescence competitive analog-based immunoassay; and solid phase chemiluminescence immunometric assay, respectively (DPC kits, Los Angeles, USA). Anti-Tg, and anti-TPO was measured by solid phase enzyme-labeled chemiluminescence immunometric assay (DPC kits, Los Angeles, USA). Intra – and inter-assay variation coefficients were less than 10% in all analyses. Reference ranges were 1.8-4.2 pg/L for fT3; 0.8-1.9 pg/L for fT4; 0.4-4.0 mU/L for TSH; <20 U/mL for anti-Tg; and <10 U/mL for anti-TPO.

All those tests were performed by the same kits in all patients irrespective to date of diagnosis. Because, the patients included into the study had test results those were performed within the previous five years of the study year. Our institution used the same kits during this period and we provided the same kits for the analyses of newly included patients.

Siemens Sonoline Sienna (Siemens, Germany) US device and 40 mm, 7.5 MHz linear probe (7.5L40, Q2000, Siemens, Germany) was used for ultrasound imaging.

Two-dimensional ultrasound estimation of thyroid volume was calculated by the ellipsoid volume formula. Width (w), length (l), and depth (d) of each thyroid lobe measured by longitudinal and transverse scans. The volume of the lobe was calculated by the formula: V (ml) = 0.479 x d x w x l (cm), as recommended by the World Health Organization (WHO) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD). Thyroid volumes were added in order to get total thyroid volume. Isthmus volume was not included into the calculation [20].

Statistical Analysis and Study Endpoints

Primary endpoint of this study was the frequency of nodular thyroid disease. Secondary endpoints were frequency of AITD, goiter, and thyroid dysfunction; and levels of fT3, fT4, TSH, and thyroid volumes.

Descriptive data were expressed as median and interquartile range (IQR), if skewed, or mean ± standard deviation (SD), if normally distributed. Log transformed levels of fT3, fT4, TSH, and thyroid volume were used to test differences between groups of patients and in healthy donors. Continuous variables were compared by Student's t-test if normally distributed. Comparison of skewed data was made by means of Wilcoxon rank-sum test. Statistical analysis of categorical variables was performed by chi-square or Fisher's exact test, when appropriate. Two-tailed p-value of less than 0.05 was defined as statistically significance level.

3. RESULTS

Thyroid Functions

Patients with CS had similar rate of thyroid dysfunctions in comparison to healthy subjects (Figure 2). Overt hypothyroidism, subclinical hypothyroidism, and subclinical hyperthyroidism was evident in 5.3% (n=1), 5.3% (n=1), and 21.1% (n=4) of patients with CS; and 2.5% (n=1), 7.5% (n=3), and 15% (n=6) of healthy subjects, respectively. 68.3% (n=13) of CS group and 75% (n=30) of control group was euthyroid. Overt hyperthyroidism was not detected in any participant.

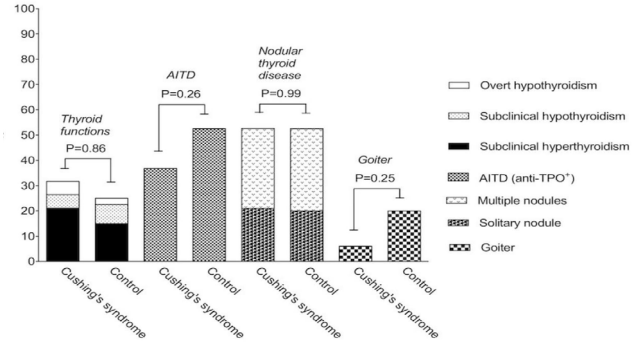

Figure 2. *Comparison of frequencies of thyroid dysfunction, autoimmune thyroid disease, nodular thy-roid disease, and diffuse goiter in patients with Cushing's syndrome and healthy subjects*

fT3 and fT4 levels were lower in patients with CS (2.41±0.79 vs 2.97±0.67 pg/L for fT3; and 1.18±0.29 vs 1.48±0.79 pg/L for fT4). There was no difference in terms of TSH between the groups (Figure 3). When only euthyroid subjects were included into the TSH comparison, groups remained comparable (P=0.63).

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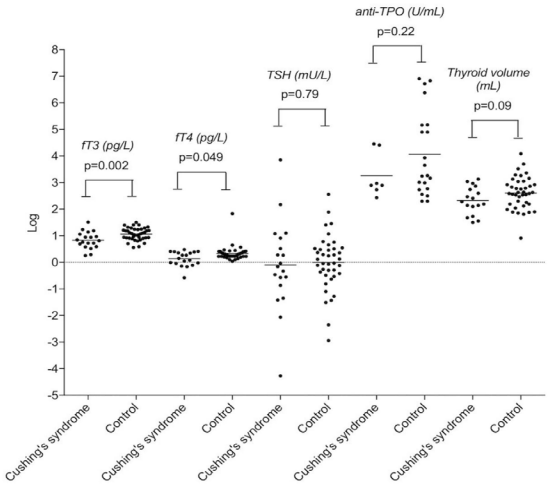

Figure 3. *Free T3 (fT3), free T4 (fT4), thyroid-stimulating hormone (TSH), anti-thyroid peroxidase (an-ti-TPO) levels and thyroid volumes in patients with Cushing's syndrome and healthy subjects have been shown. All values were log transformed*

Autoimmune Thyroid Disease

Prevalence of AITD, defined as anti-TPO positivity alone, tended to be lower (36.8% (n=7) vs 52.5% (n=21) in patients with CS (Figure 2). However, when the definition of anti-TPO$^+$/US$^+$ was used to denote AITD, none of the patients with CS had AITD. On the other hand, AITD was demonstrated in 27.5% (n=11) of the control group (P=0.01).

Among subjects with AITD (anti-TPO$^+$), having CS had no impact on serum anti-TPO titers (Figure 3). Even though we did not incorporate into the AITD definition, anti-Tg, as an autoimmune antibody, was observed 15.8% (n=3) of CS patients and 32.5% (n=13) of healthy subjects (P=0.22).

Nodular Thyroid Disease

A frequency of thyroid nodule was 52.6% (n=10) and 52.5% (n=21) in patients with CS and controls, respectively. More than half of the subjects with a thyroid nodule in each group had multiple nodules [60% (n=6) vs 61.9% (n=13), CS vs control, respectively] (Figure 2).

Goiter

Although not significant, goiter seemed to be less prevalent among patients with CS [5.9% (n=1) vs 20% (n=8)] (Figure 2). Concordantly, thyroid volumes had a tendency to be smaller in CS (11.58±5.83 vs 16.26±10.75) (Figure 3).

4. DISCUSSION

We demonstrated that the thyroid diseases including thyroid dysfunctions, AITD, nodular thyroid disease, and goiter could be detected in similar frequencies in patients with CS and healthy population. CS is associated with lower fT3 and fT4 levels, less ultrasonographic manifestations of AITD, and a tendency to have smaller thyroid sizes.

Exogenous glucocorticoids can inhibit pro-TRH mRNA in a cell-specific manner in rats. Hypothetically, these can lead to reduction in the biosynthesis and release of TRH in hypophysiotropic neurons of the paraventricular nucleus [1]. According to Tasker et al., glucocorticoids activate membrane glucocorticoid receptors in order to stimulate endocannabinoid synthesis in the hypothalamic paraventricular nucleus (PVN). Subsequently it give rise to retrograde cannabinoid type I receptor-mediated suppression of the excitatory synaptic drive to PVN neuroendocrine cells. Rapid corticosteroid actions in the hippocampus, amygdala, and pituitary are mediated by various cellular mechanisms and may also contribute to the rapid negative feedback regulation of the HPA neuroendocrine axis as well as to the stress regulation of emotional and spatial memory formation [21].

In patients with CS, pulsatile nocturnal TSH secretion is decreased due to blunting of TSH response to TRH which leads to decreased levels of thyroid hormone levels.

In CS, plasma TSH or T4 levels may be affected regardless of etiology. However, it is found that no correlation was found between the baseline cortisol and fT4 levels [1,6]. We failed to show lower levels of TSH in either whole CS cohort or in euthyroid patients with CS. Interestingly in a previous study, Onal el all., who performed a study exploring primary thyroid diseases in 38 patients with CS, also reported no difference in terms of TSH in euthyroid CS patients before and after the treatment [11].

Actually in healthy people, mean nocturnal TSH levels are 51% higher than afternoon values One of the reasons of discrepancy between the results of various studies might be affected by blood withdrawal time. Sample size differences across the studies may also give rise different results [6]. It is reported that, in CS patients, the levels of T4, T3, and FT3 are reduced and reverse T3 levels are increased. The decreased ratio of T3:T4 can be attributed to glucocorticoid-related inhibition of peripheral deiodination [6,22,23]. The nocturnal serum thyrotropin surge is abolished in patients with adrenocorticotropin (ACTH)-dependent or ACTH-independent Cushing's syndrome [18]. Our findings are consistent within this context.

We found that AITD, defined as anti-TPO$^+$, seems to be more prevalent in control group but this association is not significant. Accordingly, anti-TPO titers had a trend to be lower in patients with CS. In previous studies, AITD, defined as the autoantibody positivity, was reported in patients with CS and controls with no significant association [12,22,24,25].

Typical appearance in US imaging is also mainly due to lymphocytic infiltration and increased blood flow [26]. Hypercortisolism reduces T-cell mediated cellular immunity within the thyroid gland. However, B-cell mediated immunity is less affected and autoantibody secretion will be maintained even if the secreted thyroid antigen levels decrease. Accordingly, we detected less AITD, defined as anti-TPO$^+$/US$^+$, in CS group.

But anti-TPO positivity and titers were similar. Nevertheless, it should be considered that our study was not powered to detect AITD. The induction of autoimmunity is associated with the normalization of CS. It appears to be linked to an improvement in immunological activity, which is inhibited throughout the active phase of the disease by endogenous hypercortisolism. According to some studies, high TSH with/without low FT4 has been linked to an exacerbation of underlying autoimmune disease, as well as a decline in serum cortisol levels, which is occasionally followed by an increase in antithyroid antibody titer [14,24,27].

We found that prevalence of nodular thyroid disease is comparable to that in healthy population. In previous studies, thyroid nodules detected by US were reported to be more prevalent in patients with CS than that in healthy population [12,14]. However, Niepomniszcze *et al.* screened thyroid nodules by palpation and reported that nodule prevalence is comparable between CS and control groups (8.4% vs 2.5%, respectively, p=0.20) [13]. It is well known that nodule prevalence increases with age [28].

Another important limitation for all studies including the current study is lack of information about the iodine status of study participants. Even small differences in iodine intake within population may lead to significant differences in thyroid volume, frequency of diffuse or nodular goiter, and nodule sizes [18]. It is emphasized that thyroid size in the community may not return to normal for months or years after correction of iodine deficiency [29]. So, it is probable that the conclusions about the nodular thyroid disease in CS are biased and incidental. Even it is assumed that the prevalence of nodular thyroid disease is higher in patients with CS, perhaps patients with CS have now less time, which may not be enough for developing thyroid nodules, under hypercortisolism due to increased awareness about CS than before. Onal et al. demonstrated that the frequency of nodular goiter is 42.5% in CS patients, whereas 30% in control group. This data signifies that there is no remarkable difference between the CS patients and control subjects with respect to the frequency of nodular goiter, which is not in agreement with earlier findings [11]. These findings support our results.

Niepomniszcze *et al.* reported that 22.4% of patients with CS had diffuse goiter by palpation. In the control group, only 6.0% had goiter (P=0.008) [13]. However, our findings indicate quite the opposite (5.9% in CS vs 20% in controls, P=0.25). Two other studies performed in patients with CS do not give details about the frequency of diffuse goiter [12,14]. The traditional method for determining thyroid size is inspection and palpation. Ultrasonography provides a more precise and objective measurement of thyroid volume compared with palpation. This becomes especially significant when the prevalence of visible goiters is small [19]. Hypothetically, decreases in basal secretion, pulsatile secretion, mean pulse mass and total secretion of TSH in 24-hour measurements are supposed to result with smaller thyroid volumes and less goiter frequency [3].

The most important limitation of the current study was the limited sample size which was calculated considering the primary end-point of the study as the presence of nodular thyroid disease. That is why it should be interpreted cautiously that all other conclusions except nodular thyroid disease may be underpowered.

In conclusion, the prevalence of thyroid dysfunction, nodular thyroid disease, and goiter is comparable to healthy population. However, AITD was less prevalent in patients with CS. Although hypercortisolism has an impact on hypothalamic-hypophyseal-thyroid axis, its clinical implication does not seem to be significant.

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Compliance with Ethical Standards

Ethical Approval: Ethical approval for this study was obtained from Istanbul University, Cerrahpasa Medical, Surgical and Pharmaceutical Research Ethics Committee approved the study protocol (approval number 2226, date 20.09.2005)

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Author Contribution: TT and PK: designed the study, TT, KK, and ZT: performed the literature search and data gathering; TT, KK, ZT, HB, SA, and PK: performed the quality assessment, TT, KK, and ZT: performed the statistical analysis, and TT, KK, ZT, HB, SA, and PK: wrote the manuscript. All authors approved the final manuscript.

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