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Original Article

Graves' disease does not pose an increased risk of thyroid cancer

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Abstract

Aim: The information on increased cancer risk in thyroid nodules in the background of Graves' disease (GD) is rarely published. In GD, thyroid stimulating hormone (TSH) and TSH receptor antibody (TRAB) are held responsible for playing the key role in the enlargement of nodules and carcinogenesis. In this study, our aim was to evaluate the relationship between GD and thyroid nodules and whether GD increases the risk of thyroid cancer.

Material and Methods: TAll patients diagnosed with GD were evaluated for TRAB, anti-thyroidperoxidase (anti-TPO), anti-thyroglobulin (anti-TG), and with thyroid function tests (TSH, sT3, sT4), and thyroid ultrasonography. Fine needle aspiration (FNA) biopsy was performed on the suitable thyroid nodules.

Results: Archived records of 182 cases followed-up with the diagnosis of GD between 2008-2014 were evaluated retrospectively. Thyroid nodules were found in 38% (n=69) of the cases. The results of the FNA biopsy of 22 of the 26 (30.5%) nodules of a total of 85 nodules were benign, and 4 were indeterminate. Thyroidectomy was performed on 4 cases with indeterminate results and their pathology results revealed that the nodules were benign. In one case operated due to unresponsiveness to medical treatment, papillary thyroid carcinoma (PTC) was detected. No correlation was detected between TRAB positivity and nodule presence and nodule cytology.

Conclusion: In the background of GD, increased nodule prevalence, increased cancer risk in nodules, and the concern for poor prognosis, which have been a matter of debate in the recent years, were not confirmed in our study. We recommend the conventional approach to thyroid nodules in the background of GD.

Keywords: Graves' disease; thyroid carcinoma; thyroid nodule.

INTRODUCTION

Graves' disease is the most common type of hyperthyroidism and is accompanied by diffuse goiter (1). The majority of patients are positive for the autoantibody against TSH receptor (TRAB) and this is a specific finding for GD (2). In the previous studies, it has been reported that the prevalence of both palpable and US-detectable thyroid nodules is higher in GD than the general population (2-5). The pathogenesis of thyroid nodules in GD is not fully understood and the real causes and prevalence of thyroid cancer on this basis are still controversial (6,7). It has been reported that TRAB in GD can lead to the characteristics of hyperfunction and hyperplasia by activating thyroid adenylate cyclase like TSH does (8). Differentiated thyroid carcinomas have the functional receptors for TSH (9,10). TRAB is known to mimic the activity of TSH on thyroid cells (11). Based on this information, there is a concern for an increased risk of thyroid cancer in GD (3,12). In the literature, various rates were reported regarding the prevalence of thyroid nodules in GD. Results of the published clinical studies on the malignancy potential of these nodules were contradictory (13,14). There is no national data available on this subject.

The aim of our study was to determine the prevalence of thyroid nodules in cases diagnosed with Graves' disease and the malignancy rate of these nodules by cytopathological evaluation. Consequently, we would like to contribute to the treatment algorithm for GD.

MATERIAL and METHODS

Archived records of all cases followed up with the diagnosis of GD between 2008-2014 in the Endocrinology and

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Metabolic Diseases outpatient clinic of our hospital were evaluated retrospectively. Clinical, laboratory, radiological and pathological data of the patients were obtained from the electronic database. TSH (0.35-4.94 mU/L), sT4 (0.7-1.48 ng/dl), and sT3 (1.71-3.71 ng/L) measurements, electro-chemiluminescence immunoassay (ECLIA), anti-TG (<20 IU/ml) and anti-TPO (<5.61 IU/ml) assays, and TRAB (<1 U/L) radioimmunoassay (RIA) were performed. Thyroid US of all patients diagnosed with Graves' disease were obtained. Clinically and radiologically suspicious nodules were biopsied. The patients were operated upon the presence of an enlarged thyroid gland with malignancy or the suspicion of malignancy based on the thyroid FNA biopsy and the recurrence of Graves' disease.

This study was approved by Başkent University Medical and Health Sciences Research Committee (Project No: KA14/51).

Statistics

In the data analysis, SPSS 25.0 software was used. Student t-test was used for the comparison between continuous variables and Chi-square test was used for the analysis of non-parametric variables. Fisher's exact test was used to compare categorical variables with small sample size and Mann-Whitney U test was used under appropriate conditions, Pearson correlation analysis was used in the correlation analysis of continuous variables. A p value < 0.05 was considered statistically significant.

RESULTS

Of the 182 patients included in the study, 138 were female and 44 were male. The mean age was 46.71±15.89 years. Demographic, clinical and laboratory data of the patients are presented in Table 1. Of all patients, 38% (n=69) had thyroid nodules. The prevalence of nodules in males was significantly higher than females (52.3% vs 33.6%, p<0.05). Of the patients with nodules, 87% (n= 60) had single nodule while 13% (n= 9) were multinodular.

Table 1. Demographical, clinical and laboratory characteristics of the study group

Characteristics	n = 182
F/M, n	138 / 44
Age (mean ±SD), years	46.71±15.89
TSH (mean ±SD), µIU/ml	0.61±2.03
sT3 ng/L	15.4± 18.1
sT4 ng/dl	2.5± 3.2
TRAB (mean ±SD) U/L	44.04 ±89.14
TRAB positivity % (n)	51 (93)
Anti-TPO median (min-max) IU/ml	58.7 (1.3-338)
Anti-Tg median (min-max) IU/ml	21.3 (0.2-101)
Treatment method	
Anthyroid drug treatment % (n)	81 (147)
RAI treatment % (n)	8 (14)
Surgery % (n)	11 (21)
RAI dosage (mean ±SD), mCi	17.63 ±20.35

anti-TG: anti-thyroglobulin, anti-TPO: anti- thyroidperoxidase, M: Male, F: Female, mCi: millicurie, RAI: Radioactive iodine TRAB: TSH receptor antibody TSH: Thyroid stimulating hormone

The median maximum nodule diameter was 10 (min:3, max: 54) mm. Of the nodules, 32% were isoechoic, 33% were hypoechoic, 23% were hyperechoic and 12% had a mixed appearance. Microcalcification was detected in 32% of the nodules (Table 2).

Table 2. Morphological and cytopathological characteristics of nodules

Nodule	n = 69	p
Nodule % (n)	38 (69)	
Presence of nodule according to sex	F: %33.6 M: %52.3	P<0.05
Single nodule,n/Multinodular,n (%)	60 (87)/ 9 (13)	
Median maximum nodule diameter (min-max), mm	10 (3-54)	
Nodule echogenicity %, n		
Hypoechoic	33	
Isoechoic	32	
Hyperechoic	23	
Mixed	12	
Microcalcification prevalence %	32	
FNA Biopsy Cytology		
Benign, n	22	
Indeterminate, n	4	
Pathology		
Benign, n	21	
Malignant, n	1	

M: Male, F: Female, FNA Biopsy: Fine Needle Aspiration Biopsy

No correlation was detected between anti-TPO and anti-TG positivity and presence of nodule, presence of single or multiple nodules, maximum nodule diameter and nodule cytology (for anti-TPO p=0.23 p=0.21 p=0.48 for anti-TG p=0.7 p=0.21 p=0.62). No correlation was detected between TRAB positivity and presence of nodule (p= 0.32). No difference was detected between being TRAB-positive and being TRAB-negative in terms of the mean maximum nodule diameter (12.8 mm and 14.7 mm, respectively, p= 0.51). No correlation was detected between TRAB value and maximum nodule diameter (p=0.85).

FNA biopsy was performed on 26 of the 85 nodules of all cases (30.5%). While 22 of these were benign, 4 were indeterminate. Thyroidectomy was performed on 4 cases with indeterminate cytology and their pathologies were found to be normal.

When those with benign FNA biopsy cytology (n=22) and those with indeterminate FNA biopsy cytology (n=4) were compared, no difference was detected in terms of mean age, mean TRAB value and TRAB positivity (p=0.33 p=0.61 p=42).

Only one of the 21 cases which underwent surgery had malignancy. This case was operated since no remission was observed after receiving unindicated medical treatment for FNA biopsy prior to the operation.

DISCUSSION

In the previously performed large epidemiological studies, it has been shown that the prevalence of thyroid nodules that can be detected by palpation is approximately 5% in females, and 1% in males who live in the areas of the world with inadequate iodine (15). However, with the increased number of imaging methods, the current nodule prevalence detected by US in the normal population is 19-68%, which is very high contrary to the assumptions (16,17). At the time of studies and reviews (2,3,13,18) reporting the increased nodule prevalence in Graves' disease (4.7-15%), the prevalence of palpable nodule in the population was known to be much lower (1-5%). In our study, the prevalence of nodule in GD is consistent with the data from the normal population, with 38%. Ultrasonography is frequently used both in the diagnosis and follow-up of patients with Graves' disease. Increased nodule prevalence in GD in the previous studies can be due to the more frequent use of imaging. This indicates that the prevalence of thyroid nodules in the general population is higher than assumed.

Thyroid cancer is observed in 7 to 15% of all thyroid nodules (19-21). Risk factors for thyroid cancer are childhood, being an adult younger than 30 years of age, previous history of radiation to the neck area, family history of thyroid cancer (15). Whether Graves' disease is a risk factor for thyroid cancer has not yet been proven. Data on this subject are contradictory. In the literature, the prevalence of nodule malignancy in the background of GD varies (2.3-45.8%) (13). In a study with 557 cases in which those with operated GD were included alone (22) and in another study with 941 cases (23), increased risk of carcinoma in GD was reported compared to patients operated due to euthyroid nodular goiter. However, in another study with 2820 patients who underwent thyroidectomy (24) the prevalence of thyroid carcinoma in the background of GD was reported to be lower than the patients with euthyroid nodular goiter (20.6% vs 34%). Evaluation of operated patients in these studies could have led to certain fallacies. Since the cases were selected among high-risk patients for whom surgery was indicated, they do not reflect the overall characteristics of the GD population. The common treatment in Graves' disease is anti-thyroid treatment and radioactive iodine (RAI) treatment. The patients are rarely referred to surgery. In our study, surgery was performed on 11.4% of the patients. Malignancy was detected in only 1 (4.8%) of the 21 GD cases who were operated. Our study is more powerful in reflecting the risk of malignancy as it comprises the population with GD alone.

Resources on how thyroid cancer in the background of Graves' disease can have a much poorer prognosis are also contradictory. In a study where all patients had thyroid cancer (25) the basis of GD was not found to have a negative effect on the initial histology while it was found to be a negative factor in the prognosis. Contrary to another study which corroborates the finding that it affects the prognosis negatively (24), there are also studies reporting that it does not affect the prognosis (26). In the studies reporting its negative effect on the prognosis, the pathologies of the operated patients were evaluated retrospectively. Since this includes the high-risk case group, for whom the decision of surgery was mostly based on cytology, it does not reflect the natural character of GD. In our study, one patient had well-differentiated thyroid carcinoma. This patient was in low-risk group. Since our study comprises isoled GD population, the risk of bias is low and increased poor prognosis in GD could not be demonstrated.

In our study, no correlation was detected between thyroid autoantibodies and TRAB and nodule characteristics and FNA biopsy results. Despite the hypothesis that TRAB can have an effect on thyroid hyperplasia and nodularity with an effect similar to that of TSH (11) there are no studies in the literature demonstrating the linear correlation between TRAB levels and nodule size. This may suggest that these parameters do not contribute to nodule pathogenesis. However, certain limitations of our study might have affected the results. Retrospective design, small number of cases and absence of a control group are the important limitations of our study.

CONCLUSION

In the background of GD, increased nodule prevalence, increased cancer risk in nodules, and the concern for poor prognosis, which have been a matter of debate in the recent years, were not confirmed in our study. Our study recommends that using the conventional approach to thyroid nodules would be more rational despite the presence of a background of GD. If the FNA biopsy cytology is benign, using non-surgical treatments for GD would be logical.

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