

ORIGINAL ARTICLE

Correlation analyses of thyroid-stimulating hormone and thyroid autoantibodies with differentiated thyroid cancer

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Summary

Purpose: To investigate the feasibilities and clinical values of thyroid-stimulating hormone (TSH) and thyroid autoantibodies in predicting differentiated thyroid cancer (DTC).

Methods: 500 patients with thyroid nodules who underwent surgery for the first time in our hospital from January 2014 to December 2016 were selected, including 250 patients definitely diagnosed pathologically with DTC and 250 patients definitely diagnosed with benign thyroid nodules after operation. Serum thyroglobulin antibody (TgAb), thyroid peroxidase antibody (TPOAb) and TSH levels before operation were evaluated in both groups. According to the reference ranges of TgAb and TPOAb, they were divided into negative and positive groups. According to the TSH reference range, they were divided into decreased, normal and increased groups. Statistical analyses were conducted, respectively.

Results: The serum TgAb level in the DTC group was significantly increased compared with that in benign thyroid nodule group ($p=0.01$). The positive rate of TgAb in DTC group was also significantly higher than that in benign thyroid

nodule group ($p<0.01$). The level of serum TPOAb in the DTC group was not significantly different from that in the benign thyroid nodule group ($p=0.25$). The level of serum TSH in the DTC group was significantly increased compared with that in the benign thyroid nodule group ($p<0.01$). There was a statistically significant difference in the comparison of the distribution of TSH between the DTC group and benign thyroid nodule group ($p<0.01$). Univariate analysis showed that TgAb and TSH were correlated with DTC. Multivariate logistic regression analysis results showed that serum positive TgAb and increased TSH were significantly correlated with DTC. TSH level in DTC with cervical lymph node metastasis group was significantly increased compared with DTC without such metastasis group ($p<0.01$).

Conclusions: Increased levels of serum TgAb and TSH may be risk factors for DTC. Whether the two indicators can be used as predictors of DTC screening needs to be confirmed in large-sample prospective trials. Increased serum TSH level is closely related to DTC with cervical lymph node metastasis.

Key words: TSH, TgAb, TPOAb, thyroid cancer

Introduction

Thyroid nodule disease is the most common disease in the endocrine and metabolic systems [1]. How to correctly judge benign and malignant thyroid nodules so as to avoid unnecessary operations for patients is a problem that every clinician must face [2]. Some studies have pointed out that

surgical treatment for patients with DTC in early and middle stages can significantly improve the survival rate [3,4]. In addition, early diagnosis and timely surgical treatment are of great significance for the treatment and prognosis of thyroid cancer patients.

At present, the differentiation of benign and malignant thyroid nodules mainly depends on thyroid B-mode ultrasound, radionuclide scanning, computed tomography (CT), magnetic resonance imaging (MRI) and fine needle aspiration biopsy (FNAB), but all these methods have different disadvantages due to their own limitations, so that they cannot alone, accurately and effectively determine benign and malignant thyroid nodules [5-7]. Many authors have reported that elevated serum TSH can be used as an important early warning signal for thyroid cancer screening [8,9]. It is well-known that the abnormal increase in TPOAb and serum TgAb are common in autoimmune thyroid diseases (AITDs) and also can be seen in DTC, thyroid adenoma (TA) and nodular goiter (NG) [10]. Therefore, 500 patients with thyroid nodules who were diagnosed and operated in our hospital since 2014 were retrospectively analyzed in this study, so as to assess the correlations of TPOAb, TgAb and TSH in the serum of these patients with benign and malignant thyroid nodules, and to explore the feasibilities and clinical values of the three indicators in predicting DTC.

Methods

Patients

Patients with thyroid nodules who underwent surgery for the first time in Affiliated Hospital, BeiHua University from January 2014 to December 2016 were selected. Before operation, serum TgAb, TPOAb and TSH levels were measured, and thyroid and cervical color Doppler ultrasound was performed. After operation, all resected specimens were routinely histopathologically examined, and diagnosed with DTC or benign thyroid nodules. Exclusion criteria: patients with previous history of thyroid surgery, thyroid radiation, hyperthyroidism, hypothyroidism, subacute thyroiditis or Hashimoto's thyroiditis, or patients undergoing oral thyroid treatment prior to operation. All participants signed informed consent before the study entry. This study was approved by the ethics committee of Affiliated Hospital of BeiHua University.

Methods

Laboratory tests: three-triiodothyronine (T3), four-triiodothyronine (T4), free T3 (FT3), free T4 (FT4), TSH, TgAb and TPOAb. The above indicators were performed in the Nuclear Medicine Department using automated chemiluminescence immunoassay test. According to the reference range of serum TSH, namely TSH<0.27 μ U/mL, 0.27-4.20 μ U/mL and >4.2 μ U/mL, the cases were divided into decreased, normal and increased categories. Based on the serum TgAb reference range, namely TgAb<115 μ U/mL and >115 μ U/mL, the cases were divided into negative and positive categories.

Thyroid ultrasound: Nodule size, number of nodules, blood flow, and calcification were recorded.

Surgical records: with or without lymph node metastasis, the number of metastatic lymph nodes, size and location where metastasis occurred, with or without surrounding tissue infiltration, and with or without distant metastasis (liver, lung, bone, etc.).

Postoperative pathology: pathological typing and immunohistochemistry results.

Statistics

The included patients were divided into DTC group and benign thyroid nodule group. Data were analyzed using SPSS 20.0 software (Armonk, NY, USA). Measurement data were expressed as mean \pm standard deviation, and independent-sample rank sum test was used for intergroup comparisons. Enumeration data were analyzed by chi-square test. Univariate and multivariate logistic regression analysis were conducted to evaluate the correlations of DTC with serum level of TSH and TgAb. $P < 0.05$ showed statistically significant difference.

Results

General data in the DTC group and benign thyroid nodule group

A total of 500 patients met the criteria of this study, including 106 males (21.20%) and 394 females (78.80%). In the DTC group, there were 55 males and 195 females with an average age of 48.05 ± 13.87 years. In the benign thyroid nodule group, there were 51 males and 199 females with an average age of 49.92 ± 12.36 years. There was

Table 1. General characteristics and thyroid nodules conditions of DTC group and benign thyroid nodule group

Characteristics	Patients, n	Age (y)	Male/Female	Diameter of nodules (cm)	Single/multiple nodules
DTC group (mean \pm SD)	250	48.05 \pm 13.87	55/195	2.43 \pm 1.97	161/89
Benign thyroid nodule group (mean \pm SD)	250	49.92 \pm 12.36	51/199	3.58 \pm 2.21	110/140
t/x ²		-2.04	5.76	-4.93	13.52
p		0.68	0.00	0.00	0.00

DTC: differentiated thyroid cancer.

a significant difference in gender composition between the two groups ($p<0.01$, Table 1).

Condition of thyroid nodules in the DTC group and benign thyroid nodule group

The mean diameter of nodules in the benign nodule group was significantly longer compared with the DTC group ($p<0.01$, Table 1). The ratio of single nodules in the benign nodule group was lower than that in the DTC group ($\chi^2=13.52$, $p<0.01$, Table 1).

Comparison of serum TSH, TgAb and TPOAb levels between the two groups of patients

Serum TSH level in the DTC group was increased compared with the benign thyroid nodule group ($Z=-4.93$, $p<0.01$, Table 2). There was a statistically significant difference in the TSH distribution between the DTC group and benign thyroid nodule

group ($Z=-3.58$, $p<0.01$). The level of serum TgAb in the DTC group was increased compared with the benign thyroid nodule group ($Z=-3.28$, $p=0.01$, Table 2). The level of serum TPOAb in the DTC group was not significantly different from that in benign thyroid nodule group ($Z=-1.17$, $p=0.25$, Table 2). The difference in the positive rate of TgAb between DTC group and benign thyroid nodule group was statistically significant ($\chi^2=13.64$, $p<0.01$).

Correlation risk assessment of serum TgAb and TSH levels with DTC

Univariate analysis showed that positive TgAb [$B=1.36$, odds ratio (OR)=4.27 and $p<0.01$] and increased TSH ($B=0.98$, OR=3.14 and $p<0.01$) were correlated with DTC (Table 3). Multivariate logistic regression analysis showed that serum positive TgAb [$B=2.19$, OR=6.95, $p<0.01$ and 95% confidence interval (CI): (3.04, 15.23)] and increased TSH

Table 2. Comparison of serum TSH, TgAb and TPOAb levels between groups [median (quartile range)]

Groups	Patients, n	TSH ($\mu\text{U/mL}$)	TgAb ($\mu\text{U/mL}$)	TPOAb ($\mu\text{U/mL}$)
DTC group	250	2.89 (2.17)	151.27 (49.54)	52.17 (18.53)
Benign thyroid nodule group	250	1.86 (1.64)	31.35 (14.62)	34.42 (14.71)
Z		-4.93	-3.28	-1.17
p		0.00	0.01	0.25

DTC: differentiated thyroid cancer

Table 3. Univariate analysis of DTC with serum level of TSH and TgAb

	B	OR	OR (95%CI)	p
Positive TgAb	1.36	4.27	2.08-8.95	0.00
Increased TSH	0.98	3.14	1.69-4.83	0.00

Positive TgAb: TgAb>115 $\mu\text{U/mL}$; Increased TSH: TSH>4.2 $\mu\text{U/mL}$

Table 4. Multivariate logistic regression analysis of DTC with serum level of TSH and TgAb

	B	OR	OR (95%CI)	p
Positive TgAb	2.19	6.95	3.04-15.23	0.00
Increased TSH	0.87	2.36	1.41-4.68	0.00

Positive TgAb: TgAb>115 $\mu\text{U/mL}$; Increased TSH: TSH>4.2 $\mu\text{U/mL}$

Table 5. Correlations of serum TSH, TgAb and TPOAb levels with cervical lymph node metastasis in DTC patients [median (quartile range)]

Cervical lymph node metastasis	Patients, n	TSH	TgAb	TPOAb
Yes	30	2.89 (2.17)	151 (49)	52 (18)
No	220	2.58 (2.00)	116 (42)	44 (14)
Z		-5.27	-3.14	-2.03
p		0.00	0.32	0.48

[B=0.87, OR=2.36, $p<0.01$ and 95% CI: (1.41, 4.68)] were significantly correlated with DTC (Table 4).

Correlations of serum TSH, TgAb and TPOAb levels with cervical lymph node metastasis in thyroid cancer

TSH level in patients in DTC with lymph node metastasis group was significantly increased compared with that in DTC without lymph node metastasis group, and the difference was statistically significant ($p<0.01$, Table 5). There were no significant differences in the levels of TgAb and TPOAb between the two groups ($p>0.05$, Table 5).

Discussion

Thyroid nodules often occur in women. The incidence rate of multiple nodules is higher than that of single nodules, but the incidence rate of single nodular thyroid cancer is higher [1,2]. The incidence rate of thyroid cancer shows an increasing trend year by year, and thyroid cancer has become the fastest growing malignant tumor in recent years. The initial judgment of the nature of thyroid nodules for determining whether it is benign or malignant so as to choose the surgical treatment or further follow-up observation is an important clinical issue.

More than 90% of thyroid cancers are DTC. Patients with different differentiated histological subtypes of DTC have different clinical manifestations, metastatic pathways and pathological features (such as slow growth of papillary carcinomas, high grade of malignancy, and metastasis primarily through lymph nodes) [1]. DTC is originated from thyroid follicular epithelial cells, most of which have slow progression, but some histological subtypes of DTC are prone to extra-thyroid invasion, vascular invasion and distant metastasis with high recurrence rate and relatively poor prognosis. In the treatment guidelines on thyroid cancer, TSH is the first choice for examination. Decreased TSH indicates that thyroid nodules have functions, and the functional nodules are less likely to be malignant. In this study, statistical analysis of the level of TSH in the two groups revealed that serum TSH level in the DTC group was significantly increased compared with that in the benign thyroid nodule group, and the number of patients with increased TSH in the DTC group was significantly larger compared with the benign thyroid nodule group. Multivariate analysis also showed that the increased serum TSH is an independent risk factor for DTC. There is increasing evidence showing that elevated serum TSH concentration may provide evidence

for earlier detection of thyroid malignant tumors [8,9,11,12]. Although the underlying mechanism of this result cannot yet be completely explained, a large number of animal experiments and clinical observation results that elevated serum TSH level may be a predictor of DTC.

TgAb and TPOAb are markers of autoimmune thyroid diseases. In this study, statistical analyses of the levels of TgAb and TPOAb between the two groups revealed that the level of serum TgAb in the DTC group was increased compared with that in benign thyroid nodule group, and the positive rate of TgAb in the former was elevated compared with that in the latter. Multivariate analyses also showed that they were independent risk factors for DTC. However, there was no difference in TPOAb between the two groups. In support of this view, many studies have shown that elevated TgAb level is not only an indicator for autoimmune thyroid diseases, but also a predictor of thyroid cancer [10,13]. Some researchers held that serum TgAb may serve as an indicator for DTC monitoring [14]. Therefore, it can be concluded that serum positive TgAb can also be an important predictor of DTC, and TPOAb acts as a specific antibody of Hashimoto's thyroiditis. The results of this study showed that there was no correlation between TPOAb and DTC, but Larson et al. [15] believed that the risk of patients with Hashimoto's thyroiditis accompanied with thyroid cancer is increased, which is different from the view of this study. Therefore, the correlation between serum TPOAb level and DTC needs to be further studied.

Cervical lymph node metastasis is a risk factor for increased recurrence and decreased survival rate in DTC patients, especially in those aged over 45 years. Some cervical lymph node metastases are not detected by preoperative imaging and intraoperative examination, but are diagnosed after prophylactic central lymph node dissection and thus alter the stage and postoperative management scheme of DTC. The study results suggest that elevated serum TSH level may be closely related to DTC cervical lymph node metastasis.

In summary, serum TSH and TgAb levels are of certain clinical value for the identification of benign thyroid nodules and DTC, and increased TSH level can be used as an important risk factor for DTC, thus providing guidance for regular follow-ups, early diagnosis and interventions of patients with nodular thyroid diseases. This study was retrospective, and the number of cases was limited, so the choice of sample might be biased to some extent. Therefore, whether serum TSH and TgAb can be used as predictors of DTC screening still needs to be confirmed by large-sample prospective trials.

Conclusions

Increased TSH and TgAb levels are closely related to the occurrence and development of DTC. Preoperative serum TSH and TgAb levels may be important serological markers for predicting the risk of DTC. Lymph node metastasis in DTC pa-

tients is often accompanied with elevated serum TSH level, so it is speculated that TSH is related to metastasis outside of DTC.

Conflict of interests

The authors declare no conflict of interests.

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