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The High Proportion of Painless Thyroiditis as a Cause of Thyrotoxicosis in Korea

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Background and Objectives: The most common cause of thyrotoxicosis is Graves' disease (GD), while painless thyroiditis (PT) comes in second. In Korea, the treatment of choice for GD is antithyroid drugs (ATDs). Since most cases of PT spontaneously improve, an accurate diagnosis is very important for the proper management of patients presenting with thyrotoxicosis. **Materials and Methods:** Ninety-nine thyrotoxic patients were routinely checked with 99m Technetium (^{99m}Tc) thyroid scan except in pregnant or lactating women. We assessed the patients' clinical characteristics, serum levels of free T4 (FT4), thyroid stimulating hormone (TSH), thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TGAb), thyrotropin-binding inhibitory immunoglobulin (TBII), and findings of ^{99m}Tc thyroid scan. **Results:** Among the 99 thyrotoxic patients, 69 were diagnosed with GD and 30 had PT. All of the patients with GD, diagnosed by scan, improved clinically and the thyroid hormone returned to normal with ATDs. All patients with PT improved spontaneously without ATDs. TPOAb and TGAb were positive in 13 (43.3%) and 20 (66.7%) patients with PT, respectively. TPOAb and TGAb were positive in 45 (65.2%) and 44 (63.8%) patients with GD, respectively. TBII was positive in only 73.5% of GD, and was entirely negative in the PT group. Mean FT4 level in GD was higher than in PT, but some patients with PT showed the highest level of FT4. **Conclusion:** PT accounted for a very high proportion of thyrotoxicosis in this study. All parameters investigated such as age, sex, goiter size or nature, level of FT4, TPOAb or TGAb, and TBII were unable to differentiate GD from PT. Considering the increased proportion of PT in the current study, we recommend routine thyroid scan in all thyrotoxic patients except in pregnant or lactating women.

Key Words: Graves' disease, Painless thyroiditis, Thyroid scan, Thyrotoxicosis

Introduction

Thyrotoxicosis is a clinical syndrome that results from high concentration of thyroid hormones, and has multiple etiologies. Graves' disease (GD) is the most common cause of thyrotoxicosis in the world, and has a population prevalence of 1–2%.[1] Painless thyroiditis (PT) is regarded as a variant of postpartum thyroiditis and of chronic autoimmune thyroiditis (Hashimoto's thyroiditis). It is characterized by rapidly developing and transient thyrotoxicosis, sometimes followed by hypothyroidism, and then recovery.[2,3] In Korea, the treatment of choice for GD is antithyroid drugs (ATDs). Most cases of PT spontaneously improved. Therefore, it is important to accurately differentiate GD from PT in order for patients to receive the proper treatment. The prevalence of PT varies in between countries, ranging from 0 to 20%.[4–6] In Korea, there is no official report on the prevalence of PT. In the present study, we determined the frequency of PT in patients with thyrotoxicosis and evaluated the usefulness of 99m Technetium (^{99m}Tc) thyroid scan in differentiating between PT and GD.

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Materials and Methods

We reviewed medical records of all thyrotoxic patients who were observed by a doctor from September 2011 to November 2013 in our hospital. With the exception of pregnant and/or lactating women, patients with sub-clinical hyperthyroidism, and patients under treatment with antithyroid drug, were routinely examined with ^{99m}Tc thyroid scan. Ninety-nine patients were included. We assessed clinical characteristics such as: size and consistency of goiter; thyrotoxic symptoms; level of free T4 (FT4), thyroid stimulating hormone (TSH), thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TGAb), thyrotropin-binding inhibitory immunoglobulin (TBII); and findings of ^{99m}Tc thyroid scan. GD and PT were differentiated from each other based on the level of uptake in ^{99m}Tc thyroid scan: GD was considered if there is increased thyroid uptake, and PT was considered if there is decreased thyroid uptake with increased background signal (Fig. 1). Final diagnosis was confirmed by the natural clinical course of the disease. The thyrotoxicosis in PT was self-limiting while the thyrotoxicosis in GD was controlled by ATDs. Thyrotoxic symptoms included palpitation, tremor, heat intolerance, and weight loss. Simple fatigue without other specific symptoms of thyrotoxicosis was counted as asymptomatic.

Level of FT4, TSH, TPOAb, and TGAb were determined by chemiluminescent immunoassay with Cobas e601 (Roche Diagnostics, Mannheim, Germany). TBII was measured as TSH-binding inhibitory activity in a radioreceptor assay system using porcine TSH receptors (RIA kit; RSR Limited, Cardiff, UK). ^{99m}Tc-pertechnetate (185 MBq) was intravenously given. Serial images of the neck area were obtained over a period of 20 minutes using gamma camera system (Xeleris, GE Healthcare, WI, USA) equipped with a low energy general purpose collimator.

The normal range of FT4 and TSH were 0.93-1.7 ng/dL and 0.27-5.0 μIU/mL, respectively. The reference range of TPOAb and TGAb were 0-115 IU/mL and 0-34 IU/mL, respectively. The normal range of TBII activity was less than 15%.

All statistical analyses were performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA). Non-parametric tests were used when the data was not normally distributed. Continuous variables were compared by the Mann-Whitney test. The Pearson chi-square test was used to compare categorical variables. Differential cut-off point of GD from PT was calculated by receiver operating characteristic (ROC) curve. A p value of less than 0.05 was considered statistically significant.

Results

In total of 99 thyrotoxic patients, 69 were diagnosed with GD (mean age, 44.0±12.4 years; range, 15 to 73; 51 women and 18 men) and 30 were diagnosed with PT (mean age, 44.0±12.4 years; range, 24 to 72; 18 women and 12 men). There were no sig-

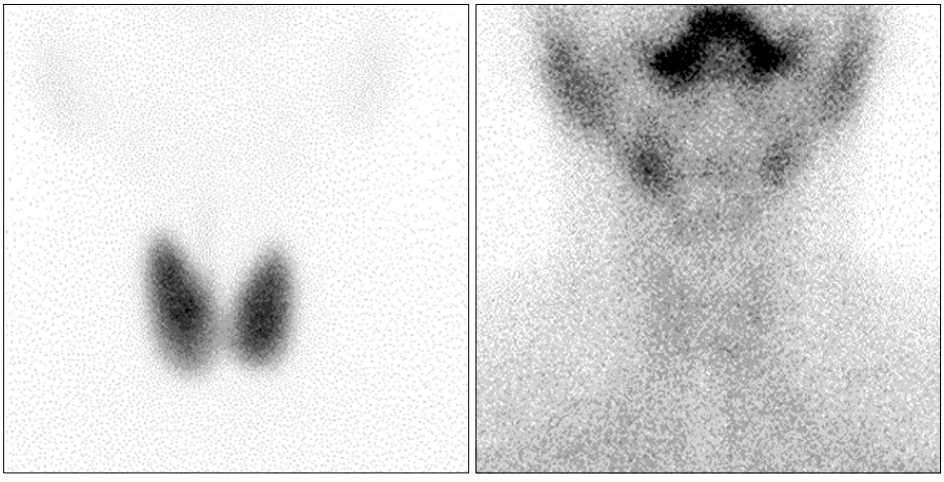

Fig. 1. Typical findings of thyroid scan of Graves' disease (left) and painless thyroiditis (right).

nificant differences in age and sex in between the two groups. The most common age at diagnosis was 40–50 years in both groups. Clinical symptoms were present in 69.6% of patients with GD and in 33.3% of patients with PT. Patients presenting with clinical symptoms was more common in GD (p=0.001) (Table 1). Thirteen out of 30 PT cases and 46 out of 69 GD cases had diffuse goiter. The consistency of the goiter in patients with GD was soft in 36 cases and hard in 10. Among patients with PT, 10 had soft goiter and 3 had hard goiter.

All patients with GD improved and their thyroid function returned to normal with ATDs. All patients with PT improved spontaneously without ATDs.

TPOAb and TGAb were positive in 13 (43.3%) and 20 (66.7%) patients with PT, respectively. TPOAb and TGAb were positive in 45 (65.2%) and 44 (63.8%) patients with GD, respectively. TGAb positive only was seen in 8 (11.9%) GD patients and 9 (30%) PT patients. TPOAb positive only was seen in 1 (1.5%) GD patient and 3 (10%) PT patients. TBII was positive in only 73.5% of GD cases, and was entirely negative in the PT group ($p<0.001$). There was slight difference in TPOAb between the two groups (p=0.042). TGAb was similar between the two groups (p=0.782) (Table 1).

Mean FT4 level in GD (mean, 4.40 ng/dL; range, 1.84–7.77) was higher than in PT (mean, 2.87 ng/dL; range, 1.72–7.77) ($p<0.001$), but 3 patients with PT showed the highest level of FT4 (Fig. 2). Total T3/FT4 ratio was significantly higher in GD (85.31± 18.74) than in PT (78.83±20.29) (p=0.044) (Table 1). The sensitivity and specificity of total T3/FT4 ratio with the cut-off value set at 75.21 were 77.0% and 60.0%, respectively (Table 2).

Table 1. Baseline characteristics of thyrotoxic patients

	Painless thyroiditis (n=30)	Graves' disease (n=69)	p value
Age (years)	44.03±12.40	44.03±12.44	0.999
Sex			0.166
Male (%)	12 (40.0)	18 (26.1)	
Female (%)	18 (60.0)	51 (73.9)	
Symptoms			0.001
Negative (%)	20 (66.7)	21 (30.4)	
Positive (%)	10 (33.3)	48 (69.6)	
Goiter			0.030
Negative (%)	17 (56.7)	23 (33.3)	
Positive (%)	13 (43.3)	46 (66.7)	
Consistency of goiter			0.918
Soft (%)	10 (56.7)	36 (78.3)	
Hard (%)	3 (23.1)	10 (21.7)	
Thyroid function test			
Total T3 (ng/dL)	213±94	369±150	<0.001
Free T4 (ng/dL)	2.87±1.68	4.44±1.84	<0.001
Total T3/Free T4	78.83±20.29	85.31±18.74	0.044
TPOAb			0.042
Negative (%)	17 (56.7)	24 (34.8)	
Positive (%)	13 (43.3)	44 (63.8)	
TGAb			0.782
Negative (%)	10 (33.3)	25 (36.2)	
Positive (%)	20 (66.7)	44 (63.8)	
TBII			<0.001
Negative (%)	30 (100)	18 (26.1)	
Positive (%)	0 (0)	50 (72.5)	

Continuous variables were analyzed by Mann-Whitney test. Categorical variables were analyzed by Pearson's Chi-square test. TBII: thyrotropin-binding inhibitory immunoglobulin, TGAb: thyroglobulin antibody, TPOAb: thyroid peroxidase antibody

Discussion

GD is the most common cause of thyrotoxicosis and accounts for 60–80% of thyrotoxicosis. PT is implicated in about 10% of thyrotoxicosis. It is not always easy to establish a definitive diagnosis of the cause of thyrotoxicosis. To complicate things further, PT can occur in patients with GD.[7] Some patients with GD have diffuse goiter of hard and nodular consistency that is commonly found in Hashimoto's thyroiditis. In this study, 13 out of 30 PT and 46 out of 69 GD had goiter. The goiter in 36 patients with GD had soft consistency and 10 were hard. Ten patients with PT had soft goiter and 3 had hard goiter. The presence of goiter or its consistency cannot effectively differentiate PT from GD.

Measurement of TSH receptor antibodies is somewhat useful for the diagnosis of GD. TSI and the first generation TBII assays are less sensitive, showing 60–90% positivity in GD.[8,9] The second generation or 3rd generation TBII assay shows positive reaction in 90–100% of patients with GD.[10–12] In this study, we used the RIA method with porcine TSH receptors that showed 100% specificity and 62% sensitivity. Some investigators[13–15] reported that 6–15% of patients with PT had positive TBII. Therefore, TBII may not be a reliable marker to differentiate GD from PT.

Previous studies reported that the total T3/FT4 ratio was useful to differentiate12 GD from PT.[16–18] Lee et al.[16] reported that the sensitivity and specificity of total T3/FT4 ratio were 75.5% and 70.3%, respectively, which was similar to what was seen in this study (sensitivity 77.0% and specificity 60%). But there was a lot of overlap between GD and PT (Fig. 3). Therefore, it cannot accurately differentiate GD from PT.

^{99m}Tc has several advantages, including short half-life (6 hours), short residence time in the gland, and absence of β-emission.[19–23] We prefer thyroid imaging with ^{99m}Tc pertechnetate because image acquisition with ^{99m}Tc is much faster than with ^{123}I or ^{131}I. After detection of thyrotoxicosis, a differential diagnosis

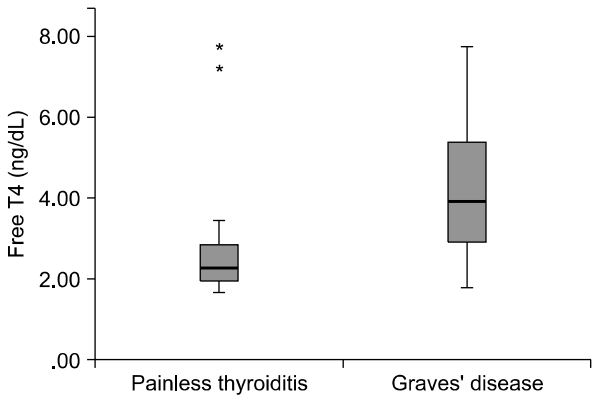

Fig. 2. The mean FT4 level of Graves' disease was higher than painless thyroiditis. The normal range of FT4 was 0.93–1.7 ng/dL. Three of 30 patients showed very high level of FT4 in PT and 5 of 59 patients showed highest level of FT4 in Graves' disease.

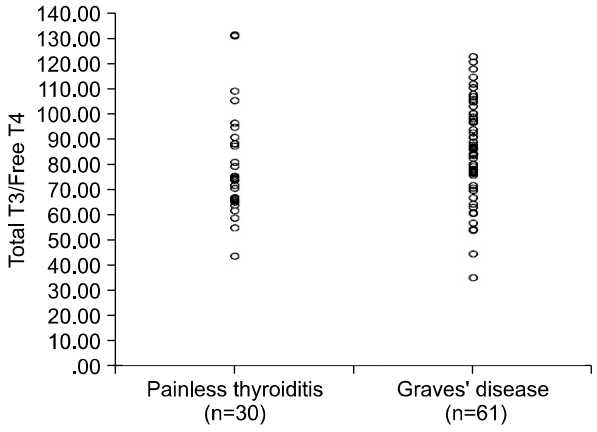

Fig. 3. Individual serum total T3/free T4 ratios in Graves' disease and painless thyroiditis. Total T3/free T4 ratio in patients with Graves' disease was significantly (p=0.044) higher than that in patients with painless thyroiditis.

Table 2. The sensitivity and specificity of differential cut-off point of Graves' disease from painless thyroiditis

	AUC (%)	Cut-off point	Sensitivity (%)	Specificity (%)
Total T3 (ng/dL)	85.0	233.5	83.6	80.0
Free T4 (ng/dL)	80.9	3.21	67.2	86.7
Total T3/Free T4	63.1	75.21	77.0	60.0

AUC: area under the curve

can be made through ^{99m}Tc thyroid scan within 20 minutes. Our data suggest that ^{99m}Tc thyroid scan is useful in the differential diagnosis of thyrotoxicosis and can be used to make a decision for immediate treatment.

Prevalence of PT among thyrotoxic patients has a wide variance: from 0% in Philadelphia, USA; 1% in Cardiff, UK, Denmark and Australia; 10% in Toronto, Canada; up to 20% in the Midwest, USA.[4-6] This wide variation in prevalence may be related to iodine intake.[10] Korean population tends to have a high iodine intake. In Korea, there is no official report of the frequency of the various causes of thyrotoxicosis. According to a report of one national university hospital in Korea, the proportion of PT (including postpartum thyroiditis) in thyrotoxicosis was 2.5% in 1990, but it has increased to 13.3% in 2006.[24] During the period of our study, there were 14 cases of subacute thyroiditis, 9 cases of postpartum thyroiditis, and 3 cases of toxic nodule in patients with thyrotoxicosis. Therefore, the proportion of PT was 30/116 (25.8%), which was very high. The reason for the increasing frequency of PT in Korea is not clear. The thyrotoxic symptoms in PT are usually milder than those in GD. Thus, many cases of PT can be missed. These days, Koreans are well covered by public insurance, and patients can visit local clinics or hospitals easily, and routine health check-up is increasing. Consequently, routine check-up of thyroid function test is increasing as well, resulting in the detection of more cases of milder thyrotoxicosis. In this study, 13 patients were detected by routine check-up: 8 patients had PT and 5 had GD. Three patients were also detected during preoperative examination (GD; 1 and PT; 2). Environmental contamination such as air pollution, water contamination, nuclear exposure, etc. may be other reasons for the increasing incidence of PT.

TPOAb and TGAb were positive in 43.3% and 65.2% of patients with PT, respectively. TPOAb and TGAb were positive in 66.7% and 63.8% of patients with GD, respectively. TGAb positive only was seen in 8 (11.9%) patients with GD and in 9 (30%) patients with PT. Many guidelines recommend the use of TPOAb for detection of autoimmune thyroid disease.[25] But, in this study, TGAb is equally or more frequently positive in autoimmune thyroid disease compared to TPOAb.

Conclusion

PT accounted for a very high proportion of thyrotoxicosis in this study. All patient parameters tested such as age, sex, goiter size or nature, level of FT4, TPOAb or TGAb, and TBII cannot effectively differentiate GD from PT. Therefore, it may be useful to order routine thyroid scan in all thyrotoxic patients except in pregnant or lactating women.

Key Message

1. Painless thyroiditis accounted for a high proportion of thyrotoxicosis in Korea.
2. Routine thyroid scan may be needed to differentiate between Graves' disease and painless thyroiditis.

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