Turkish Journal of Endocrinology and Metabolism, (2000) 4 : 119-122 **ORIGINAL ARTICLE**

Thyrotropin Receptor Antibody Levels in Patients with Autoimmune Thyroid Disease in Iodine Deficient Areas

Demet Çorapçıoğlu Arif Ender Yılmaz Vedia Tonyukuk Mehmet Baştemir Rifat Emral Sevim Güllü Ali Rıza Uysal Nuri Kamel Gürbüz Erdoğan

Department of Endocrinology and Metabolic Diseases, Ankara University School of Medicine, Ankara, Turkey

In this study, we investigated Thyrotropin Receptor Antibody (TRab) levels in Hashimoto and Graves' diseases. A total of 189 patients and 25 controls were assessed, retrospectively. Fifty-four of the 189 patients had euthyroid Hashimoto thyroiditis and the remaining group had Graves' disease. In order to assess the TRab level differences in the subgroups, patients with Graves disease were subdivided into 4 groups according to their clinical status and the presence of ophthalmopathy as follows: hyperthyroid Graves' disease without ophthalmopathy (Group A, n=16); hyperthyroid Graves' disease with ophthalmopathy (Group B, n=43); euthyroid Graves' disease without ophthalmopathy (Group C, n=28); and euthyroid Graves' disease with ophthalmopathy (Group D, n=48). The incidence of positive TRab assay in the Hashimoto group was 7.4% (ranged 0.15-21.00), whereas 62% were positive in the Graves' group (range 0.007-187.1). By means of TRab titers there was no statistical difference found between the Hashimoto group and the control group. In group A, TRab was detected in 12 patients (75%) and in group C, in 22 patients (51%). In groups B and D, TRab was detected in 22 patients (80%) and 28 patients (59%) respectively. It can be concluded that as a practical method, TRab assay may be useful in making a differential diagnosis of Graves' disease rather than other Autoimmune Thyroid Diseases (AITD's), for patients who show no signs of ophthalmopathy and/or hyperthyroidism.

Key words : TSH receptor antibody (TRAb), Autoimmune Thyroid Disease (AITD), Graves' disease

Introduction

The diagnosis of Graves' hyperthyroidism is relatively easy to make and is based upon positive laboratory tests, clinical symptoms, and signs, when present (1). However, a small percentage of patients with Graves' disease present with neither with hyperthyroidism, nor with signs of ophthalmopathy and the diagnosis can therefore be difficult to make in these patients. As mentioned in a European multicenter study, a "full picture" of Graves' disease occurs in only 10% of patients (2). Moreover, in the same study, 31% of hyperthyroid patients could not be classified as having Graves' disease. Although it is easy to diagnose Graves' disease when a clinical hyperthyroid state and ophthalmopathy are present, there can still be some difficulty in diagnosing some patients, especially when laboratory tests such as the radioiodine uptake and/or the scanning of the thyroid gland are falsely negative.

Correspondence address:

Demet Çorapçıoğlu
İbn-i Sina Hastanesi
Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı,
10. Kat D-Blok 06100 Samanpazarı, Ankara, Turkey
Tel: 310 33 33/2955 - 2100 Fax: 309 45 05
E-mail: demeter@superonline.com.tr

TRab (Thyrotropin receptor antibody) is a well-known marker of thyroid gland autoimmunity and may have some predictive value in the recurrence of Graves' disease after treatment with antithyroid drugs (3). Although not recommended as a first line test in the diagnosis of Graves' disease, the TRab assay is more sensitive than a homogeneous thyroid scan and a palpation of a diffusely enlarged gland (89% versus 78.1% and 74.8 %) (1). In some studies the specificity of the TRab assay comes close to 98-100% and the sensitivity ranges from 60-90% (4,5) in iodine sufficient areas. But it is controversial whether the sensitivity and specificity of the TRab assay could be found so high as to predict a diagnosis in iodine deficient areas, like our country. As Davis and colleagues (1) mentioned, in iodine deficient areas, it could be difficult for TRab to induce thyroid hormone release because of the lack of intrathyroidal iodine in patients with Graves' disease.

The aim of this study is to assess the sensitivity of the TRab assay in the diagnosis of patients with Graves' disease in Turkey which is known as an iodine deficient area, and to compare the results of the patients with Hashimoto thyroiditis and the control groups. Also we assessed the correlation of TRab levels and clinical thyroid status in patients with Graves' ophthalmopathy and we compared the results with the data collected from the patients with Graves' disease without ophthalmopathy.

Patients and Methods

One hundred and eighty nine patients from a moderately iodine deficient central Anatolian area of Turkey, mainly from Ankara, admitted to the Endocrinology and Metabolism Outpatient Clinic between October 1998 and March 1999 were examined retrospectively. Hyperthyroid patients with a presence of ophthalmopathy and/or dermatopathy, a positive thyroid peroxidase antibody (anti-TPO), and increased radioactive iodine uptake (RAIU) with a diffusely enlarged thyroid gland were diagnosed as having Graves' disease whereas patients with a decreased radioactive iodine uptake (RAIU), euthyroid, or a hypothyroid state and a positive anti-TPO antibody were diagnosed as having Hashimoto disease. Fifty-four of 189 AITD patients had euthyroid Hashimoto thyroiditis. None of the patients with Hashimoto disease were hyperthyroid and none of them had ophthalmopathy at the sampling time. The remaining group had Graves' disease (n=135). Also 25 healthy subjects were taken as a control group for assessing false positive TRab test results. The Graves' group was subdivided into 4 groups according to their clinical status and the presence of ophthalmopathy. Group A: Hyperthyroid Graves' disease without ophthalmopathy (n=16), Group B: Hyperthyroid Graves' disease with ophthalmopathy (n=43), Group C: Euthyroid Graves' disease without ophthalmopathy (n=28), Group D: Euthyroid Graves' disease with ophthalmopathy (n=48). TRab was determined by a radioreceptor assay (RRA) using a commercially available kit (IMMUNOTECH «Anti R-TSH» radioreceptor assay kit). The test was considered positive when the binding inhibition of 125l-thyrotropin was more than 15%. Anti TPO was measured by hemagglutination using a commercially available kit. Proptosis was evaluated with a Hertel exophthalmometer. If a value greater than 19 mm was obtained, it was accepted as proptosis (9). Graves' ophthalmopathy was diagnosed with orbital MRI in patients with orbital symptoms and signs and was graded using a clinical activation score defined in the literature (11).

Data are expressed as mean ± SD or median (range). All calculations were performed with SPSS (SPSS, Chicago, IL). The Spearman's Rank Correlation Coefficient was done in order to asses the relationship between TRab and anti TPO levels. A 'ci-square'-test was used for comparison of TRab titer levels measured in groups. A p value <0.05 was considered statistically significant.

Results

There was no difference between groups according to F/M ratio and age ($p>0.05$). In 135 patients with Graves' disease the mean serum concentration level of TRab was 30.7% (0.07-187.1), which was significantly higher than in the Hashimoto group and the control groups ($p<0.05$) (Figure 1). In the Hashimoto group a mean TRab titer value of 5.1% was observed, which was not significantly different from the control group value (5.8%) ($p>0.05$). Regardless of the presence of ophthalmopathy patients with hyperthyroid Graves' disease had the highest mean TRab titer (39.46 ± 6.6) ($p<0.05$) (Table 1). The mean TRab titer in euthyroid Graves' patients, however was 26.58%, which was still significantly higher than both the Hashimoto group and the control groups ($p<0.05$) (Table 2). The mean TRab titer in the ophthalmopathy group did

not differ significantly from the group in which ophthalmopathy was not present in patients with Graves' disease (p>0.05). In both Graves' disease groups with ophthalmopathy and without ophthalmopathy, TRab assay was well correlated with anti-TPO levels.

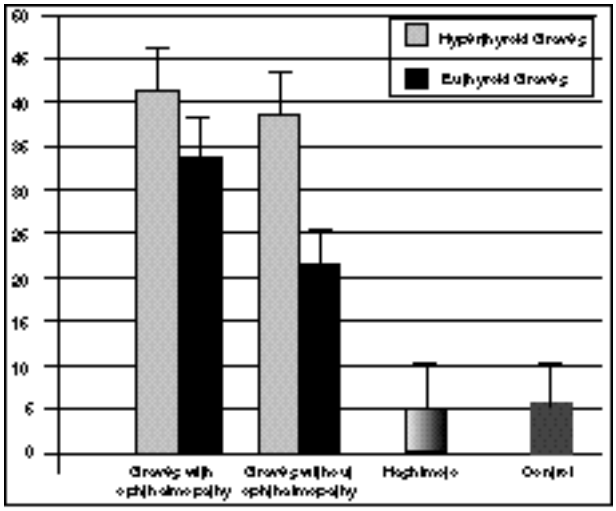

Figure 1. Mean TRab titers in the assessed subgroups of AITD and in the control group. TRab titer level didnot differ according to ophthalmopathy in the Graves' disease group (p>0.05), but was significantly higher in the Graves' group than in the Hashimoto and control groups (p<0.05).

Table 1. Mean TRab titers in hyperthyroid and euthyroid Graves' disease groups.

	n	TRab % (Mean ±SD)	p value
Hyperthyroid Graves' Disease	59	39.46 ± 6.6	p <0.05
Euthyroid Graves' Disease	76	26.58 ± 6.5	

Table 2. Mean TRab titers and incidence of positive TRab assay in groups A, B, C, and D.

	N	TRab % (Mean ±SD)	Percentage of Positive TRab Titer	p value
Hyperthyroid				
No-GO*				
Group A	16	38.5 ± 5.6	75 (n=12)	p<0.05
GO**				
Group B	43	41.3 ± 7.4	80 (n=34)	p<0.05
Euthyroid				
No-GO				
Group C	28	21.1 ± 5.6	51 (n=14)	p<0.05
GO				
Group D	48	33.5 ± 7.4	59 (n=28)	p<0.05
Hashimoto	54	5.1 ± 4.8	7.4(n=4)	p>0.05
Control	25	5.8 ± 1.2	0.0	

* Patients without Graves Ophthalmopathy,

** Patients with Graves Ophthalmopathy.

P value indicates the statistical significance of difference, from the control group.

Discussion

Although the measurement of the serum TRab concentration is not recommended as a first line test (1), clinical findings, the measurement of the anti TPO, and a radio iodine uptake of the thyroid cannot always give sufficient evidence to diagnose Graves' disease in some patients, so it can be important in the diagnosis of Graves' disease. In our study, the sensitivity and specificity of the TRab assay in patients with Graves' disease was 78% and 94.9%, respectively. Many authors have reported the sensitivity and specificity of their TRab assay being between 81% and 100%, respectively (5,6). Our data is correlated with this finding and confirms the high sensitivity and specificity.

As mentioned in other studies in the literature, the prevalence of a positive TRab assay was much lower in our patients with Hashimoto disease than in those with Graves' disease (7). Practically, this finding may be helpful in distinguishing these two AITD especially when clinical and laboratory findings are insufficient in confirming the diagnosis of Graves' disease. Moreover, the detection of TRab may have some beneficial predictive value in assessing clinical remission. TRab titers are found to be well correlated with clinical thyroid status in our patients. It could be estimated that rather than normalization, a falling TRab titer would be more reasonable for predicting remission in treatment with antithyroid drugs. Some authors claimed that in iodine-deficient areas the ability of TRab to induce hyperthyroidism would be difficult because of the lack of intrathyroidal iodine and so it would not be expected to see a good correlation between TRab and hyperthyroidism (1). In fact, in our study, there is a good correlation between TRab titer and hyperthyroidism in Turkey, where iodine-deficiency is prevalent. On the other hand, we didnot find any difference between the presence and the absence of ophthalmopathy in respect to TRab titer. This finding may be due to measured inhibitory type immunoglobulins in the TRab assay. As Yoshimura and colleagues (12), mentioned that Thyroid-Stimulating Antibody rather than TSH binding inhibitor immunoglobulin, is related to Graves' ophthalmopathy. As a result, the assay of TRab is an easy, practical, and sensitive method for diagnosing and assessing Graves' disease, even in iodine-deficient areas, especially for

those patients whose clinical state and laboratory do not demonstrate enough clues.

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