Graves' Disease and Diagnostic Approaches

Graves Hastalığında Tanısal Yaklaşım

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Abstract

Although thyroid stimulating hormone receptor antibody (TSH-Rab) is pathogonomonic for Graves' disease, antibodies against thyroglobulin, thyroperoxidase can also be detected in serum of patients. Many authors propose that ophtalmopathy and/or dermopathy are sufficient for diagnosis. This study is designed to investigate our diagnostic approaches for Graves' disease. In 860 patients with suppressed TSH levels, among cases with thyroiditis and hyperthyroidism; presence of ophtalmopathy or radioactive iodine uptake (RAIU) over 30% at 24th hour or presence of TSH-Rab was defined as Graves' disease. In cases exhibiting similar features; co-existence of at least two of the following were diagnosed as possible Graves' disease; heterogenous or increased activity at scintigraphy, antibodies other than TSH-Rab, RAIU between 20-30%, young age, typical clinical course. Patients without Graves' disease had hyperactive nodules or heterogenous or suppressed activity at imaging with at least two of the following; older age, atypical clinical course, negative auto-antibodies, RAIU below 20%. One-hundred twenty-eight patients (14.9%) had Graves' disease, 107 (12.4%) possible Graves' disease, 625 (72.7%) were without Graves' disease. Both Graves' groups had similar gender and age distribution ($p>0.05$). They were younger than the rest and had smaller glands. *Turk Jem 2007; 11: 7-9*

Key words: Graves' disease, Thyroid stimulating hormone receptor antibody (TSH-Rab), thyrotoxicosis

Özet

Tiroid uyarıcı hormon reseptör antikoru (TSH-Rab), Graves hastalığı için tanı koydurucudur. Etkilenen olguların serumlarında tiroglobulin ve tiroperoksidaza karşı antikorlar da saptanabilir. Pek çok araştırıcı, oftalmopati ve/veya dermopati varlığını tanı için yeterli görmektedir. Bu çalışma, Graves hastalığı teşhisinde kullandığımız tanısal yaklaşımları değerlendirmek üzere planlanmıştır. Serum TSH düzeyleri baskılanmış olan 860 olgu alt gruplara ayrılarak incelenmiştir. Tiroiditi olan olgularda; oftalmopati varlığı veya TSH-Rab varlığı veya 24. saatte tiroid yatağında radyoaktif iyot tutulumunun (RAIU) %30'un üzerinde olması 'Graves hastalığı' olarak tanımlanmıştır. Yine tiroiditi olan olgularda, belirtilecek durumlardan en az ikisinin birlikte olması; tiroid sintigrafisinde heterojen veya aralık seyri 'muhtemel Graves hastalığı' olarak değerlendirilmiştir. Sintigrafik incelemede hiperaktif nodül veya heterojen veya baskılı görüntü saptanmasına, belirtilecek maddelerden en az ikisinin eşlik etmesi; ileri yaş, tipik olmayan klinik seyir, otoantikorların izlenmemesi veya RAIU'nun %20'nin altında olması, 'Graves hastalığı olmaması' olarak yorumlanmıştır. Yüzyirmisekiz (%14.9) olgu 'Graves hastalığı', 107 (%12.4) olgu 'muhtemel Graves hastalığı' ve 625 (%72.7) olgu 'Graves hastalığı olmayanlar' şeklinde gruplanmıştır. Her iki Graves grubunun yaş ve cinsiyet dağılımı benzerdir ($p>0.05$). Bu olgular, Graves hastalığı olmayan gruptan daha gençtir ve tiroid bezleri daha küçüktür. *Turk Jem 2007; 11: 7-9*

Anahtar kelimeler: Graves hastalığı, Tiroid uyarıcı hormon reseptör antikoru (TSH-Rab), tirotoksikoz

Introduction

Graves' disease is the leading cause of hyperthyroidism worldwide (1). The mechanisms involved in suspectibility to Graves' disease are supposed to be a mixture of genetic, environmental and endogenous factors that rise humoral and cellular auto-reactivity against thyrotropin receptor. It shares many immunological features with autoimmune hypothyroidism. Although thyroid stimulating hormone (TSH) receptor antibody (TSH-Rab) is a patognomonic finding, antibodies against thyroglobulin (ATA), thyroperoxidase (anti-TPO) and sodium iodide co-transporter can be detected in the serum of many patients. Female: male ratio is 5-10:1, reminding the modulation of autoimmune response by estrogen. Ophtalmopathy and dermopathy are specific findings for the disease. The clinical course of hyperthyroidism is usually characterized by relapses and remissions. Radioactive iodine uptake (RAIU) at 24th hour is typically high (2-4).

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Diagnosis of Graves' disease is generally based on clinical and biochemical manifestations of hyperthyroidism. Ophtalmopathy and/or dermopathy are reported to be sufficient to confirm the diagnosis of Graves' disease in a patient with hyperthyroidism and diffuse goiter. However, there has not been an approved systematic approach for the diagnosis (4). Some clinicians use routine tests; thyroid ultrasonography and scintigraphy, plus clinical specific signs for the diagnosis, whereas, some may choose to perform specific tests such as; TSH-Rab and/or RAIU at 24th hour.
In the present study, we aimed to investigate our diagnostic approaches for Graves' disease.

Materials and Methods

The medical records of 860 patients, admitted at our outpatient clinics with suppressed TSH levels from 1998 through 2003 were evaluated retrospectively. The term of suppressed TSH was used for TSH measurements below 0.3mU/L. Active thyroid glands imaged by scintigraphy or radioactive iodine uptake (RAIU) test at 24th hour were defined as hyperthyroidism, whereas, suppressed activity was regarded as thyrotoxicosis (5). Differential diagnosis was further carried by studying the morphological findings at thyroid ultrasonography, evaluation of clinical features, such as age at onset, clinical course of the disease and presence of Graves' ophtalmopathy and/or dermopathy and determination of thyroidal auto-antibodies where needed.
In a patient with thyroiditis and hyperthyroidism, presence of Graves' specific ophtalmopathy and/or dermopathy or RAIU test over 30% at 24th hour or detection of TSH-Rab was solely accepted to be sufficient for the diagnosis of Graves' disease. Co-presentation of at least two of the followings were defined as possible Graves' disease among patients with thyroiditis and hyperthyroidism; heterogenous or increased activity at scintigraphy, detection of antibodies other than TSH-Rab, RAIU levels between 20-30% at 24th hour, younger age at onset, typical clinical course resembling Graves' disease. Patients without Graves' disease were the ones who had hyperactive nodules or heterogenous or suppressed activity at scintigraphy with at least two of the follow-ings; older age at onset, atypical clinical course for Graves' disease, negative serum autoantibodies, RAIU below 20% at 24th hour.
Thyroid volumes of all patients were calculated via ultrasonographic measurements of each lobe by using the ellipsoid formula. (ellipsoid formula: length x depth x width x π/ 6 for each lobe) (6).
Statistical analyses were performed using SPSS for windows, version 9.05. They were conducted at the $p<0.05$ level of significance. Student t-Test, Chi-square Test and One-Way Anova Test were used when appropriate.

Results

Among 860 patients with suppressed TSH levels, 625 (72.7%) did not have Graves' disease, 128 (14.9%) had Graves' disease and 107 (12.4%) had possible Graves' disease. Three groups exhibited similar distribution regarding gender.
Cases without Graves' disease were older than the rest of the group ($p=0.000$). The two Graves' groups were of the same age. Cases without Graves' disease had larger volumes than the others. There was a statistically significant difference between Graves' groups regarding thyroid volume. Patients with possible Graves' disease had smaller volumes ($p=0.032$). The details are shown in Table 1.
Among Graves' disease group, 58 (45.3%) of the patients exhibited ophtalmopathy. Thyroid-stimulating hormone receptor antibody measurements were performed in 11 (4.7%) of the two Graves' groups (n=235); 9 of them had TSH-Rab positivity. It was performed due to academic purposes on six patients with ophtalmopathy and was found to be high with increased RAIU levels. Low number of cases with TSH-Rab measurement limited us to perform statistical analysis.
One-hundred-nine (85.1%) patients among Graves' disease group had auto-antibody measurements other than TSH-Rab. The procedure was need not to be performed on 11 (8.59%) cases who exhibited ophtalmopathy.

Discussion

Hyperthyroidism is a serious health issue, resulting in many clinical problems, such as atrial fibrillation, increased left ventricular mass and diastolic dysfunction (7). The incidence of Graves' disease seems to increase as a consequence of induction of thyroidal autoimmunity by the exposure to excess iodine via salts and richly iodinated sources of industrialization (8-10). Diagnostic algorithm for Graves' disease may vary among physicians. In a patient with thyroiditis and hyperthyroidism, some physicians may choose to perform diagnosis via routine scintigraphy and specific clinical signs, while, some may use additional advanced procedures, such as TSH-Rab measurement and RAIU (4). Latter techniques are usually

Table 1. General features of the patients regarding diagnosis

Patients (Pts) (n=860)	**Pts without Graves' disease n=625, 72.7%)**	**Pts with Graves' disease (n=128, 14.9%)**	**Pts with possible Graves' disease (n=107, 12.4%)**	**p**
Men/Women (n)	179 / 446 (28.6%/ 71.4%)	30/98 (23.4%/ 76.6%)	27/ 80 (25.2%/ 74.8%)	>0.05 NS
Age (years)	55.37 ± 14.39 (17-91)	40.59 ± 13.28 (15-75)	43.64 ± 13.29 (17-80)	=0.000
Thyroid volume (cm3)	37.96 ± 34.83 (3.53-211.99)	27.30 ± 22.02 (2.58-170.0)	21.93 ± 11.44 (6.71-57.84)	=0.000

performed for academic purposes and/or indeterminate characteristics of some patients.

In this study, the two Graves' groups; ones with Graves' disease and the ones with possible Graves' disease exhibited similar age and gender distribution. Their mean ages were younger and thyroidal volumes were smaller than the rest of patients who were diagnosed as the ones without Graves' disease. They seem to be the representatives of the same disorder. Six-hundred twenty-five patients without Graves' disease were the ones dominantly having nodules and this finding might explain their larger volumes (11).

Although TSH-Rab measurements were performed in a limited number of patients, high serum levels were detected among patients with ophtalmopathy or with high RAIU at 24th hour. This procedure seemed to be performed due to academic rather than diagnostic purposes.

Depending on our results, we may propose that except in case of extraordinary presentations or findings, the diagnosis of Graves' disease may be performed by the help of clinical observations and imaging procedures routinely used for differential diagnosis of suppressed TSH levels. Taking into account the huge amount of money we pay for diagnostic methods, we believe that Graves' disease can be diagnosed via routine tests.

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