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Grave's Disease: An Analysis of Thyroid Hormone Levels and Hyperthyroid Signs and Symptoms

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The diagnosis of hyperthyroidism is suspected in the setting of thyrotoxic symptoms and confirmed by standard thyroid function tests[1]. There is a wide variation in the magnitude of symptoms as well as in the level of thyroid hormones. Thyroid function test results may be markedly abnormal when the patient is only minimally symptomatic, or conversely, may be modestly elevated at the same time that the patient exhibits classic symptoms[1-4]. Thus, it has been suggested that the intensity of thyrotoxic symptoms does not correlate with the degree of elevation of thyroid function tests[2]. This discrepancy may arise if serum levels do not reflect intracellular thyroid hormone concentrations, if there are cellular variations in nuclear thyroid hormone receptor sensitivity[3], or if some hyperthyroid symptoms are adrenergically mediated[5,6]. In addition, previous studies have not specifically addressed this issue using standardized symptom rating scales to assess and quantify the severity of symptoms.

To further clarify this clinically important question, we prospectively studied 25 hyperthyroid patients using a previously described standardized symptom rating scale[7] and serum thyroid function tests to investigate the relationship between symptom severity and the degree of hormone elevation. We have also compared the severity of psychiatric symptoms with these parameters.

PATIENTS AND METHODS

Twenty-five subjects with untreated, newly diagnosed Graves' disease were consecutively recruited. Subjects with other significant medical diseases, pregnancy, substance abuse, or a pre-existing major psychiatric disorder were excluded. The duration of hyperthyroid symptoms anamnestically reported by the subjects ranged from six to eighteen months.

Procedure

A complete medical history and physical examination were performed. Clinical estimates of goiter size in grams were independently made by an endocrinologist. Electrocardiography was used to determine heart rate. Serum thyroid function tests included the total serum triiodothyronine T3, thyroxine T4, and TSH IRMA by radioimmunoassay (RIA). Normal ranges for TT3, TT4, and TSH IRMA of RIA are given in the Table listed below. The Hyperthyroid Symptom Scale (HSS)[7], which quantitatively measures 10 different hyperthyroid parameters, was independently completed by the examining endocrinologist, and their total scores were averaged. The HSS has been shown to be a valid and sensitive measure of clinical thyrotoxic symptoms. This scale is useful to judge patient improvement during the course of treatment and differentiates treated from untreated states. The HSS rates 10 items on 0-4 point subscales, including sweating, heat tolerance, nervousness, hyperactivity, tremor, weakness, hyperdynamic precordium, diarrhea, appetite, and degree of incapacitation. Because of the high prevalence of psychiatric symptoms in hyperthyroidism[8,9], we also measured symptoms of anxiety and depression.

RESULTS

Subjects

Twenty-one subjects were women and four were men. This sex ratio reflects the prevalence of Graves disease. Their ages ranged from 19 to 61 years with a mean of 35.6±12.1 (SD) years. All subjects had elevated thyroid function test results. Their mean T3 RIA was 4.18±1.2 ng/mL (range, 2.5 to 6.84 ng/mL). All had a diffusely enlarged thyroid without nodules. Their mean goiter size was 58.4±14.8 g, which is about three times greater than normal, and their mean heart rate was 104.6±13.6

beats/minute. All subjects had typical symptoms of thyrotoxicosis. Their mean HSS score was 26.3±5.1 points, a value that is significantly greater than that for normal subjects or for hyperthyroid patients who have been treated with propranolol or antithyroid regimens[7].

Rationship of symptom ratings and signs with hormone levels

The thyroid function tests were significantly correlated with T3 RIA (r = 0.61, p = 0.002) and goiter size (r 0.65, p 0.001), and inversely correlated with age (r = -0.43, p = 0.02). A similar relationship between T3 RIA and goiter size (r = 0.44, p = 0.02) and age (r = -0.60, p = 0.002) was also observed. Since T3, T4 and IRMA TSH RIA strongly correlate with age, regression analysis was used to study the linear relationship between measures of various symptoms and thyroid hormone levels. These regression analyses reveal that none of the endocrine or psychiatric symptom ratings, or heart rate, was significantly related to thyroid horome levels.

DISCUSSION

We have rated hyperthyroid signs and symptoms, and depressive and anxious symptoms in 25 subjects with untreated, newly diagnosed Graves' disease using standarized rating scales[7,10-13]. Using regression analyses, controlling for age, we found that the severity of symptoms was not linearly related to thyroid hormone levels. Only goiter size was significantly related to TT3, TT4 and IRMA TSH by RIA. Our data suggest that the clinical expression of thyroid hormone activity is not simply related to measured serum levels of thyroid hormones. This is not entirely surprising given prior clinical impressions that thyroid function testing alone does not predict the severity of clincial expression of thyroid disease[1,4]. In our study, all subjects had an elevation of thyroid hormone levels as well as the presence of a number of endocrine symptoms.

Despite this lack of association between symptoms and serum thyroid hormone levels, we did find a significant correlation between advanced age and milder levels of some peripheral symptoms. That we found less sweating, heat intolerance, and hyperactivity, as well as less overall incapacitation by the hyperthyroidism in consistent with previous descriptions of "apathetic" hyperthyroidism in the elderly[14]. Nordyke et al[15] found that hyperthyroid symptoms decreased gradually afer the fifth decade. We observed no difference in cardiovascular symptoms (heart rate or hyperdynamic precordium) at different ages[14] although an increase in atrial fibrillation has been reported in older patients[15].

The severity of peripheral endocrine symptoms, as measured by the HSS, was correlated with goiter size, and correlated highly with thyroid hormone levels. The severity of peripheral endocrine symptoms correlated with the severity of anxiety. This relationship is consistent with hyperthyroidism as a common cause of organic anxiety syndrome. It is possible that variations at the receptor level could account for the differences in the degree of hyperthyroid signs and symptoms seen in various individuals. Anxious and depressive symptoms are often part of the presenting clinical picture in hyperthyroidism. Catecholamines may play a major role in the pathophysiology of anxiety and affective disorders[16]. Thus, some of the peripheral endocrine and central nervous system thyrotoxic symptoms may also be related to changes in catecholamines induced by elevated thyroid hormone levels[16].

In summary, the present study suggests that there is no relationship between the clinical assessment of disease severity and serum levels of thyroid hormone in untreated Grave's disease. This study also sugggests potential variables such as cellular responsiveness to thyroid hormone and/or catecholamines and their resultant effect to produce hyperthyroid symptoms contributing to the lack of a linear relationship between serum thyroid hormone levels and severity of thyrotoxic symptoms.

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