Relapse of Graves' Disease After Medical Therapy: Predictive Value of Thyroidal Technetium-99m Uptake and Serum Thyroid Stimulating Hormone Receptor Antibody Levels

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In 49 patients with Graves' disease, the 20-min thyroidal uptake of ^{99m}Tc and serum levels of thyroid stimulating hormone (TSH) receptor antibody were estimated at presentation and at intervals during a 1-yr course of carbimazole and triiodothyronine. In the 12 mo after cessation of therapy, 29 patients developed recurrent thyrotoxicosis. Thyroidal ^{99m}Tc uptake had a poor predictive value for recurrence of thyrotoxicosis, both at presentation and during therapy. A very high level of TSH receptor antibody was present in seven patients at presentation, all of whom relapsed on withdrawing therapy. An abnormal value of TSH receptor antibody at the end of the course of medical therapy was present in 24/29 (83%) patients who relapsed and in 1/20 (5%) patients who remained euthyroid 1 yr after stopping antithyroid drugs.

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Antithyroid drugs are effective in controlling the clinical and biochemical manifestations of hyperthyroidism in patients with Graves' disease. However, when they are withdrawn, even after a prolonged course of administration, a proportion of patients will develop recurrent thyrotoxicosis. The incidence of relapse after medical therapy varies greatly in different series but is usually of the order of 50–70% (*1,2*). The ability to identify patients who will relapse after stopping antithyroidal drugs would be useful as it would indicate individuals who require long term antithyroid drugs or thyroid ablative therapy.

Clinical features have proven to be unreliable in predicting which patients will relapse after withdrawal of antithyroid drugs and levels of thyroid hormones either at presentation or during medical treatment have no discriminant value (*3*). The measurement of early thyroidal trapping of radioactive iodine (*4*) or technetium-99m (^{99m}Tc) (*5*) has been proposed as a useful predictor, with individuals who subsequently relapse showing a failure of uptake to suppress during a combination of antithyroid drug and triiodothyronine administration.

An alternative approach has utilized measurement of serum levels of immunoglobulins which bind to thyroid stimulating hormone (TSH) receptors. Such immunoglobulins are a heterogeneous group which may either stimulate thyroid activity or block the action of TSH. The stimulating and blocking antibodies can be differentiated by the effect of the patient's serum on adenylate cyclase activity in thyroid cell tissue culture (*6*). More commonly TSH receptor antibody (TSH Ab) levels are estimated by measuring inhibition of binding of radiolabeled TSH to detergent solubilized thyroid membranes in vitro (*7*). This type of assay does not quantify what proportion of the TSH Ab is stimulatory to the thyroid.

In the present prospective study, we have compared

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TABLE 1
Mean Values (±s.d.) of Serum Total Thyroid Hormone Levels at Presentation and After 12 mo Antithyroid Therapy*

	Presentation		12 mo	
	Gp I	GP II	Gp I	Gp II
Serum total T_4 (nmol/l)	247.2 (±40.3)	255.5 (±46.2)	40.6 (±25.5)	47.6 (±28.5)
Serum total T_3 (nmol/l)	8.4 (±2.9)	9.4 (±3.8)	—	—

* $p > 0.05$ for GpI vs. GpII in each case, Wilcoxon.

the ability of serial estimations of thyroidal ^{99m}Tc uptake and serum levels of TSH Ab to identify individuals with Graves' disease who would relapse after a 1-yr course of antithyroid drugs.

PATIENTS

Forty-nine patients (5 male, 44 female), ranging in age from 16–51 yr (mean ± s.d. = 36.8 ± 12.1) were studied. All patients were clinically and biochemically thyrotoxic, and in 48 the presence of diffuse hyperplasia of the thyroid was confirmed by a ^{99m}Tc thyroid scan performed at the time of presentation.

Each patient received a standardized treatment regime, consisting of carbimazole 15 mg tds for 1 mo, carbimazole 10 mg tds for 1 mo and then carbimazole 10 mg bd plus triiodothyronine (T_3) 20 mcg tds or qds for 10 mo. Each patient was followed for 12 mo after stopping medical therapy.

MATERIALS AND METHODS

Thyroidal ^{99m}Tc uptake

Thyroidal trapping of ^{99m}Tc was measured 20 min after the i.v. injection of 0.22 mCi (8MBq) [^{99m}Tc]pertechnetate. Measurements were performed using a unidirectional probe touching the anterior neck. By use of a neck phantom and a standard prepared from the dose given to the patient, a percentage uptake was calculated. Correction for background activity was not performed. The normal range in our laboratory for subjects taking no thyroid medication is ≤3%. Uptake measurements were performed at presentation and at 3, 6, 9, and 12 mo after starting therapy.

TSH radioreceptor assay

Immunoglobulins were extracted from serum samples by precipitation with polyethylene glycol (30% W/V). All samples were then made up to a standard concentration of 10 mg/ml before being assayed for TSH Ab activity according to the method of Shewring and Smith (*8*). The result obtained was converted from % bound to an index using the formula:

$$100 \times \left[1 - \frac{\%\text{ bound in test sample}}{\%\text{ bound in mean normal value}}\right]$$

the normal range in our laboratory being −25 to +25.

TSH Ab assays were performed at presentation and at 3, 6, 9, and 12 mo after starting therapy.

Thyroid hormone levels

Serum levels of total thyroxine (T_4) and total triiodothyronine (T_3) were performed by radioimmunoassay (*9*) at presentation and at 3, 6, 9 and 12 mo after starting therapy. The normal ranges for the laboratory are T_4 55-144 nmol/l and T_3 0.9–2.8 nmol/l.

RESULTS

At the end of 12 mo follow-up, 20 patients (Group I) remained clinically and biochemically euthyroid while 29 patients (Group II) had developed recurrent thyrotoxicosis confirmed by elevated serum thyroid hormone levels.

The serum total T_4 and total T_3 levels at the time of presentation and the serum total T_4 levels after 12 mo of antithyroid therapy did not differ significantly between the two groups (Table 1). Triiodothyronine values at 12 mo have not been reported since all patients were receiving T_3.

The mean value of thyroidal ^{99m}Tc uptake did not differ significantly between Groups I and II at any time during the 12 mo of medical therapy (Table 2). The individual values for ^{99m}Tc uptake at presentation and after 12 mo of antithyroid therapy are plotted in Fig. 1 and show the considerable overlap of values in the two groups of patients.

At presentation, detectable levels of TSH Ab were found in 46/49 (94%) patients. The mean value of TSH Ab index was significantly higher in Group II than in Group I at presentation and at the time of all subsequent estimations during medical therapy (Table 3).

TABLE 2
Mean Values (±s.d.) of 20 min Thyroidal ^{99m}Tc Uptake at Presentation and at Stated Time After Starting Antithyroid Drugs

Time	Group I	Group II
Presentation	12.6 (±8.4)	12.4 (±9.4)*
3 mo	7.4 (±5.6)	12.7 (±10.2)*
6 mo	6.4 (±5.6)	8.3 (±5.7)*
9 mo	6.3 (±3.7)	10.8 (±3.7)*
12 mo	6.9 (±5.2)	8.8 (±6.5)*

* $p > 0.05$, GpI vs. GpII, Wilcoxon.

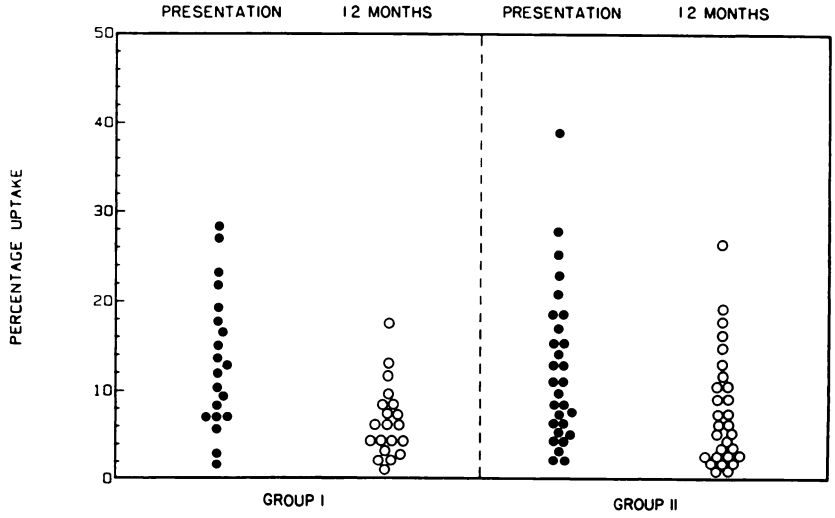

FIGURE 1
Individual values of 20-min thyroidal ^{99m}Tc uptake at presentation and after 12 mo antithyroid therapy

The individual values for TSH Ab index at presentation and after 12 mo of therapy are plotted in Fig. 2. At presentation, seven patients had a TSH Ab index >80. All seven subsequently relapsed. The sensitivity and specificity of an abnormal TSH Ab index (>25) for predicting relapse at each time of estimation are detailed in Table 4.

DISCUSSION

One year after the cessation of a 12-mo course of antithyroidal drugs 20/49 (41%) of our patients remained euthyroid. This rate is similar to that found in other series (*1,2*). The patients who relapsed did not differ clinically in any consistent fashion from those who remained in control. In keeping with the findings in other studies, the serum thyroid hormone levels either at presentation or after 12 mo of medical therapy could not be used to identify which patients would relapse when antithyroid drugs were withdrawn.

We have been unable to confirm that the 20-min uptake of ^{99m}Tc is useful in identifying individuals who will relapse after antithyroid therapy. Values of ^{99m}Tc uptake tended to be higher in Group II at all times after starting medical therapy but at no point was the difference between Groups I and II statistically significant. In both groups, the mean value for uptake fell during therapy, and at 12 mo the overlap between the groups remained considerable (Fig. 1). At the time of stopping therapy, 12 patients had a ^{99m}Tc uptake of >10%. Nine of them subsequently relapsed. However, of the 37 patients with an uptake <10% at this time, 20 subsequently relapsed. We therefore believe that the 20-min ^{99m}Tc uptake is of insufficient predictive value to be clinically useful in identifying patients who will relapse in the 12 mo after stopping medical therapy.

Our findings on the lack of value of the ^{99m}Tc uptake are in conflict with those of Alexander et al. (*4*) who have found that the 20-min uptake of radioiodine 6 mo after starting therapy could be used to identify the patients who were likely to relapse. More recently Gossage et al. (*3*) have reported that the mean value of ^{99m}Tc uptake was higher after 12 mo of carbimazole in patients who subsequently relapsed than in those who remained in remission 12 mo after stopping the drugs. They found, however, considerable overlap between the two groups. Wilkins et al. (*10*) also found considerable overlap in values between those who relapsed and those who did not. Once again, however, the mean values were higher in the group who eventually relapsed.

Our results indicate that the estimation of serum

TABLE 3
Mean Values (±s.d) of Serum TSH Receptor Antibody Index at Presentation and After Starting Antithyroid Drugs

Time	Group I	Group II
Presentation	40.3 ± 17.5	59.8 ± 22.3*
3 mo	26.8 ± 14.4	49.8 ± 19.3*
6 mo	21.2 ± 17.3	36.8 ± 27.5*
9 mo	10.9 ± 10.1	38.5 ± 27.8†
12 mo	11.4 ± 8.7	39.1 ± 22.2†

* $p < 0.05$, Gp I vs. Gp II, Wilcoxon.
† $p < 0.01$ Gp I vs. Gp II, Wilcoxon.

TABLE 4
Predictive Value of an Abnormal Serum TSH Receptor Antibody Index at Presentation and at Intervals After Starting Antithyroid Drugs

Time after therapy started	Sensitivity	Specificity	Overall accuracy
Presentation	24/29 (83%)	1/20 (5%)	25/49 (51%)
3 mo	24/29 (83%)	12/20 (60%)	36/49 (73%)
6 mo	22/29 (76%)	12/20 (60%)	34/49 (69%)
9 mo	23/29 (79%)	15/20 (75%)	38/49 (78%)
12 mo	24/29 (83%)	19/20 (95%)	43/49 (88%)

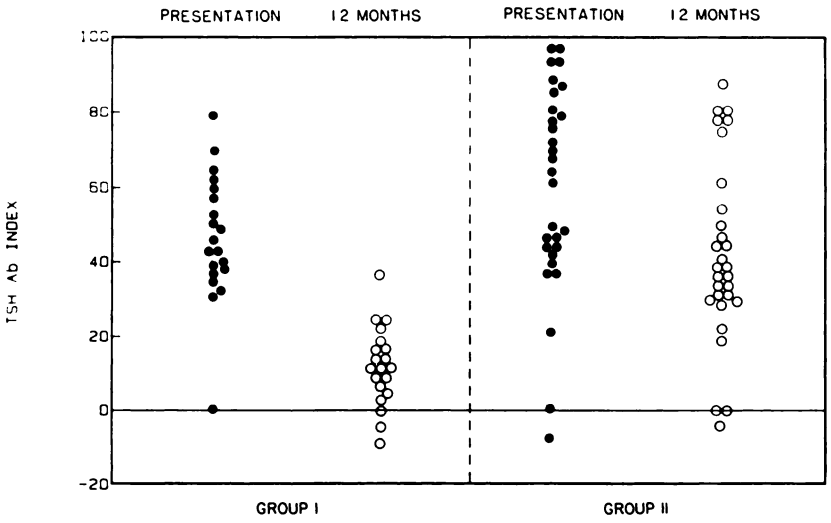

FIGURE 2
Individual values of serum TSH receptor antibody (TSH Ab) at presentation and after 12 mo antithyroid therapy

levels of TSH Ab at the end of 12 mo of medical therapy is useful in identifying patients who are likely to develop recurrent thyrotoxicosis within the next 12 mo. Assuming an abnormal TSH Ab index (>25) to indicate relapse, the 12-mo value of serum TSH Ab had a sensitivity of 83% and a specificity of 95% at an overall accuracy of 88%. If the three patients with undetectable TSH Ab are excluded, the sensitivity is 24/27 (88%) and the specificity 18/19 (95%) to give an overall accuracy of 42/46 (91%). The values at presentation were of less help. All seven patients with a TSH Ab index of >80 at presentation relapsed when antithyroid therapy was stopped. A very high TSH Ab value at presentation, however, identified only 7/29 (24%) of the eventual relapses. The levels of TSH Ab at intervals during administration of medical therapy showed gradually increasing discrimination between patients who would subsequently relapse and those who would remain in remission, mainly attributed to a fall in values into the normal range in patients who remained in remission. The predictive value of an abnormal TSH Ab index at 6 mo in our study is similar to that found by McGregor et al. (*11*) who estimated serum levels of TSH receptor antibodies in thyrotoxic patients at the end of a 6-mo course of therapy.

The proportion of Graves' disease patients in the present study with an elevated level of serum TSH Ab is similar to that found in some of the previous studies reported in the literature (*12–14*). Although in other series, a smaller percentage of patients had abnormal values at presentation (*15–17*). It is unclear whether this variation in the percentage of abnormal values at presentation represents differences in patient populations or in the assays used for TSH Ab.

There has also been considerable controversy over the predictive value of an abnormal TSH Ab level on cessation of therapy. The percentage of abnormal TSH Ab levels on cessation of therapy in patients who developed recurrent thyrotoxicosis has ranged from 54% (*15,17*) to 92% (*13*) and in those who remained in remission from 0% (*17*) to 50% (*15*).

In summary, the present study has prospectively evaluated the role of early thyroidal uptake of ^{99m}Tc and serum levels of TSH Ab in identifying which patients with Graves' disease are likely to relapse when a 12-mo course of antithyroid drugs is completed. Our results for ^{99m}Tc uptake demonstrate such a marked overlap between patients who relapsed and those who did not that we believe it is of little value in this context. TSH Ab levels at presentation are of limited value, though a small proportion of patients will have very elevated values that appear to be associated with a high probability of relapse. The discriminatory value of TSH Ab levels increases during the period of antithyroid drug therapy and reaches an overall accuracy of around 90% after 12 mo of treatment.

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