ORIGINAL ARTICLE

The prognostic significance of thyroid antibodies in patients with hyperthyroidism treated with Carbimazole

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ABSTRACT

Introduction: Measurement of antithyroglobulin (TgAb) and antithyroperoxidase (TPOAb) antibodies have been performed widely for the clinical diagnosis of autoimmune thyroid diseases. The presence of antibody markers will provide the physicians an idea of the long term prognosis and the patients can be counselled accordingly.

Objectives: The aim of the present study was to monitor the clinical significance of serum TgAb and TPOAb during and after treatment with Carbimazole in hyperthyroidism.

Materials and Methods: Seventy six patients were treated for two years and then followed for an additional one and a half year. The patients were classified into the following groups: group I, patients negative for both TgAb and TPOAb before and during the two years of treatment, group II, patients positive for TPOAb but negative for TgAb before and during the two years of treatment and group III, patients who were positive for both TgAb and TPOAb before and during therapy. The antibody markers were estimated by immunoradiometric and radioimmunoassay methods.

Results: The relapse rates after discontinuation of treatment in these groups were 45% (9 of 20), 32% (10 of 31) and 17% (4 of 23) respectively; the value in group I was significantly higher than that in group III ($p<0.01$). The results suggest that the presence of TPOAb and TgAb may influence the prognosis of hyperthyroid patients treated with carbimazole.

Conclusion: We conclude that the relapse rate in drug-treated patients who had positive antithyroid antibody titres (TgAb and TPOAb) was lower than that in patients in whom both tests were negative. [IJEM 2007;(3&4):11-13]

Key Words: Thyroid antibodies (TgAb and TPOAb), hyperthyroidism, carbimazole, autoimmune thyroid disease

INTRODUCTION

Autoimmune thyroid disease (AITD) is characterised by the presence of circulating autoantibodies directed to thyroid antigen. The majority can be diagnosed by clinical presentation and their antibody profiles to thyroglobulin (TgAb) and thyroid microsomes (TPOAb). Thyroid microsomal antibodies have been recently proven to be directed to thyroid peroxidase (TPO) and at least some TPO antibodies inhibit the formation of thyroid hormones(1). In a survey of disease free population conducted by the National Health and Nutrition Examination III, USA it was found that a large proportion of US population unknowingly have laboratory evidence of thyroid disease which supports the usefulness of screening of T4, TSH and thyroid antibodies for early detection(2). Diagnostic evaluation of AITD by a sensitive radioimmunoassay for serum TPOAb has been reported by us(3). In our earlier observation we had demonstrated that among the normal population in Eastern India, TgAb was positive in 7.7% and TPOAb in 9.2% and the positivity were more prevalent in women than men with increasing age group(4). About 20% of patients with hyperthyroidism due to Graves' disease developed hypothyroidism subsequent to discontinuation of antithyroid drug therapy(5,6). In such patients the thyroid destruction was thought to be due to autoimmune mechanisms and/or the presence of TSH-blocking antibodies(5). Controversy exists regarding the relapse rate in-patients with Graves' disease who had high serum TgAb and TPOAb titres(7,8). To investigate further the clinical significance of thyroid antibodies in hyperthyroidism, we determined the results of antithyroid drug therapy in hyperthyroid patients subdivided according to their TgAb and TPOAb status and during therapy.

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MATERIALS AND METHODS

A total of 91 participants (15 normal and 76 patients) were recruited for this study. Normal sera were obtained from 15 healthy subjects-10 female and 5 male, aged between 19 and 56 yrs). Pathological sera were obtained from 76 patients with previously untreated hyperthyroidism visiting the thyroid and medical clinics. There were 14 men and 62 women aged between 20 and 54 yrs. Hyperthyroidism was diagnosed on the basis of medical history, clinical findings, serum thyroid hormone levels and thyroidal ^{131}I uptake study. Goiter size was estimated by palpation followed by both initial and periodical neck girth assessment during follow-up. In the present series, 58 hyperthyroid patients had definite ophthalmopathy and thus could be classified as Graves' disease patients. The other 18 patients had diffuse goitres with no nodules in them. However, the cause of hyperthyroidism could not be determined with certainty.

Thyroid function tests

The 24 hr thyroidal ^{131}I uptake (normal range 20-45%) was measured by a standard method as approved by Radiation Medicine Centre, Bhaba Atomic Research Centre, Mumbai. Serum T3, T4 and TSH concentrations were estimated in duplicate using RIA kits obtained from Bhaba Atomic Research Centre, Mumbai. Serum free T4 (FT4) level was measured by a RIA kit obtained from Institute of Isotopes Co. Ltd, Budapest. The normal ranges were 0.7 to 2.0 ng/ml, 5.5 to 13.5 mg/dl, 0.25 to 5.0 to 13.5mg/ml and 12 to 23 pmol/l respectively.

Measurement of antithyroid antibodies

Serum TgAb was determined by a 'sandwich' immunoradiometric method and TPO-Ab by a RIA method with protocol and kits obtained from M/S Immunotech, a Beckman Coulter Company, France. The assay sensitivities for TgAb and TPO-Ab are 10.0 U/ml and 15.0 U/ml respectively. The intraassay coefficient of variation were 5.8 and 8.1 respectively using 10 serum replicates. The healthy normal subjects exhibit, below 100.0 u/ml and 50.0 u/ml values for TgAb and TPO-Ab respectively.

Treatment protocol

The patients were treated for a period of two years with carbimazole and were followed for at least one and a half year after termination of treatment [18 to 38 months, mean 26.5±6.8 (SD) months]. The thyroid function tests were normal in all patients when treatment was discontinued. Relapse of hyperthyroidism was diagnosed on the basis of clinical history and physical finding, elevated serum thyroid hormone concentrations and increased 24 hrs thyroidal ^{131}I uptake. The initial doses of carbimazole were 30mg daily and thyroid function was evaluated every month. The carbimazole dose was gradually decreased as the serum thyroid hormone levels declined to normal but in no patient for whom data were included here was it discontinued before two years had elapsed. Serum TgAb and TPO-Ab titres were also measured every month. During the two-year period of treatment, the patients who were initially and continued to be TgAb and TPO-Ab negative were classified into group I (21 patients). Group II (31 patients) consisted of those patients who were initially and continued to be TgAb negative and TPO-Ab positive during two year of treatment. Group III (24 patients) consisted of those patients who were initially and continued to have positive titres for both TgAb and TPO-Ab. One patient who was positive for both the antibodies initially became negative for TgAb during therapy and one patient who was negative for both the antibodies initially became positive for TPO-Ab only during therapy. Since these two patients did not fit into the above three groups they were eliminated from the study. Comparisons were made among the groups with respect to thyroid function at the time of initial medical examination, relapse rate, initial goiter size and time from discontinuation of therapy to relapse. The relapse rate between individual groups were compared statistically and $p<0.05$ was considered significant.

RESULTS

The patients' initial thyroid antibody levels according to the classification of different groups are shown in Table l. Serum thyroid hormone levels in three groups at the time of their initial evaluation are shown in Table 2. The results did not differ significantly among the groups. Table 3 shows the mean relapse rate, initial goiter size, times between discontinuation of treatment and diagnosis of relapse after at least one and a half year of discontinuation of treatment in the three groups. The mean goiter size and the time period

Table 1: Initial serum thyroid autoantibody levels in different groups of hyperthyroid patients

Groups	TgAb (U/ml)	TPOAb (U/ml)
I (n=21)	72.6±11.3	39.4±5.2
II (n=31)	81.5±7.2	185.8±21.7
III (n=24)	190.6±32.5	232.5±29.4
Normal (n=15)	41.3±14.5	23.7±10.5
Normal limit	<100.0	<50.0

Figures in parenthesis indicate number of subjects
Results are in mean±S.D.

Table 2: Initial thyroid function tests in patients with hyperthyroid state

Group	Serum T3 (ng/ml)	Serum T4 (mg/dl)	Serum TSH (m/ml)	Serum FT4 (pmol/L)	I^{131} uptake 24 hr (%)
I (n=21)	3.1±1.02	14.5±1.2	0.21±0.06	28.5±3.2	58.3±9.1
II (n=31)	4.2±1.1	16.4±1.3	0.24±0.08	34.0±5.1	66.5±8.7
III (n=24)	3.7±1.4	15.6±1.5	0.19±0.1	30.7±4.4	62.8±7.6
Normal (n=15)	1.3±0.28	8.5±1.1	1.7±0.45	16.4±2.2	32.0±4.2
Normal range	[0.72- 2.0]	[5.5-13.5]	[0.25-5.0]	[12-23]	[20-45]

Figures in first bracket indicate number of subjects
Results are in mean±S.D

Table 3: Relapse rate (RR), initial goiter size and time between discontinuation of carbimazole and diagnosis of relapse

Group	No.of Cases	No. of Relapse	RR (%)	Initial goiter size (g)	Time from discontinuation of therapy to relapse (Months)
I	20	9	45	33.5±9.0 (18-50)	15.4±3.6
II	31	10	32	40.6±1.0 (22-65)	12.8±4.5
III	23	4	17	42.3±10.0 (23-62)	14.5±3.7

Results are in mean±S.D

between discontinuation of therapy and relapse were almost similar. However, the relapse rates among the three groups differed significantly ($p<0.05$). Pairwise comparison revealed that the relapse rate in group I was significantly higher ($p<0.01$) than that in group III but the rates in group I and II were not statistically significant. Among 54 patients who were positive for TPO-Ab (group II and III), 14(25%) relapsed. This relapse rate was significantly lower ($p<0.05$) than that (45%) in the group I with persistently negative TPO-Ab titres. When the patients were classified on the basis of the presence or absence of TgAb, 4 of 2.1 patients (17%) of TgAb positive cases and 19 of 51 (37%) of the TgAb negative patients had relapsed ($p<0.02$). Three patients (1 in group I and 2 in group III) underwent subtotal thyroidectomy after they had relapsed and then had received carbimazole therapy. Lymphocytic infiltration and destruction of follicular structures were noted in the thyroid tissues obtained in two patients who had positive titres for both TgAb and TPO-Ab. In one patient whom both the titres were negative, no thyroid lymphocytic infiltration was seen and there was less destruction of follicular structure.

DISCUSSION

The evolution from hyperthyroidism to hypothyroidism probably results from thyroid destruction induced by autoimmune mechanism (TgAb, TPO-Ab) and /or TSH - blocking antibodies(5). Indeed, marked lymphocytic infiltration and destruction of follicular structures were found in this study in the thyroid tissues obtained at the time of subtotal thyroidectomy of patients who were TgAb and TPO-Ab positive. The higher incidence of hypothyroidism after subtotal thyroidectomy in Graves' disease with positive TPO-Ab had already been reported (9).

In our study a significantly lower rate of relapse of hyperthyroidism occurred in those patients who were positive for both TgAb and TPO-Ab, compared to those who had negative titres for both antibodies. The likely mechanism for the difference is that those patients with both positive titres had some antibody-mediated destruction of thyroid cells. Our findings are in agreement with earlier study(10) but contradict with other studies(7,8). The significance of TgAb remains controversial, some reports indicate that TgAb do not manifest antibody-dependant cell-mediated cytotoxicity similar to that of antimicrosomal (TPO-Ab) antibodies(10,11,12) whereas other reports maintain that Tg-TgAb action can mediate cytolysis of thyroid cells(13,14). Our result support the contention that decreased thyroid function in patients with hyperthyroidism previously treated with an antithyroid drug is probably due to the destruction of thyroid tissue resulting from the presence of TgAb and Tro-Ab. We conclude that the prognosis for long term remission in carbimazole-treated hyperthyroid patients is better who have elevated serum TgAb and TPO-Ab concentrations.

CONCLUSION

We conclude that the relapse rate in drug-treated patients who had positive antithyroid antibody titres (TgAb and TPOAb) was lower than that in patients in whom both tests were negative.

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