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Remission of Grave's disease after oral anti-thyroid drug treatment

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ORIGINAL ARTICLE

Remission of Grave's Disease After Oral Anti-Thyroid Drug Treatment

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ABSTRACT

Objective: To evaluate remission rate of anti-thyroid drug treatment in patients with Grave's disease, and to study the factors associated with remission.

Study Design: A cross sectional study.

Place and Duration of Study: The Endocrine Department of the Aga Khan University Hospital, Karachi from 1999 to 2000.

Methodology: Seventy four patients of Grave's disease were recruited who were prescribed medical treatment. Graves' disease was diagnosed in the presence of clinical and biochemical hyperthyroidism along with anti-microsomal (AMA) and anti-thyroglobulin antibodies (ATA) and thyroid scan. These patients were prescribed oral anti-thyroid drugs using titration regime and followed at 3, 6, 12 and 18 months. Patients were categorized into two groups: "remission group" and "treatment failure group" and results were compared using a chi-square test, t-test and logistic regression model with significance at $p < 0.05$.

Results: A majority of the patients were females (62.6%, n=46). During the follow-up period of 18 months, 41.9% patients went into remission. Univariate analysis showed that the initial free T4 level was significantly different ($p < 0.05$) in patients in remission and treatment failure groups. Multivariate analysis showed only initial free T4 level was a significant predictor of outcome. Positive AMA patients (n=27) had higher treatment failure (odds ratio: 2.55: 95%, CI 0.69 – 9:31), although the difference was not statistically significant ($p = 0.13$).

Conclusion: Remission rates with oral anti-thyroid agents is markedly high. Patients should be offered alternate treatment options to those who do not enter remission during a period of 12-18 months of treatment, those who develop relapse, and those who have aggressive disease on initial presentation.

Key words: *Graves disease. Oral anti-thyroid medication. Remission. Free T_4 level.*

INTRODUCTION

Grave's disease is the commonest form of hyper-thyroidism affecting women 5-10 times more frequently than men.[1] There is auto-immunity against the thyroid-stimulating hormone (TSH) receptor as the central pathogenetic element. The disease may have a number of clinical manifestations, the most common being thyrotoxicosis caused by generation of TSH receptor activating autoantibodies (Graves' hype-rthyroidism). There are three main methods of treatment of Grave's hyperthyroidism; radioactive iodine (RAI), oral anti-thyroid medication and surgery. Most physicians prefer the first one in United States, while antithyroid drugs are preferred in Europe.[2-4]

The two drugs in common use for the treatment of Grave's disease, are methimazole (MMI) and propylthiouracil (PTU). They are both thionamides and exert their anti-thyroid effect by inhibition of thyroid peroxidase catalysed synthesis of thyroid hormones. Thereby, thyroid hormone secretion gradually diminishes, and the patient becomes euthyroid. Although thionamides are highly effective in controlling hyperthyroidism, long term remission is obtained only in 30-50% of patients.[5-7] Moreover, it has been proven from different clinical studies, that radioactive iodine treatment results in the cure of Grave's hyperthyroidism and is therefore now considered a preferred treatment.[8] Considering the fact that thionamides have a high chance of failure, most of the patients still prefer anti-thyroid drugs for the treatment of Grave's hyper-thyroidism, probably due to fear of radioactivity and greater initial cost.

In developing countries, including Pakistan, physicians treating Grave's hyperthyroidism mostly use anti-thyroid drugs, as the first line treatment. The relapse and remission rates of this treatment have not been studied so far in the local population. Therefore, this study was carried out to evaluate remission rates in the patients of Grave's hyperthyroidism treated with thionamides, and to study the factors associated with the remission in these patients.

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METHODOLOGY

Seventy four adult patients of Grave's hyperthyroidism were recruited, over the period of 1999 and 2000, from the Endocrinology Clinic at the Aga Khan University Hospital, Karachi, Pakistan. These patients were given thionamides as a medical treatment for Grave's disease. Carbimazole was used as a thionamide drug, which is equivalent to Methimazole. Graves' disease was defined as the presence of clinical and biochemical hyperthyroidism (elevated serum T4 or more specifically free T4 concentration and undetectable TSH) with an elevated diffuse thyroid uptake seen in 99mTc-pertechnetate scan. If an uptake scan were not available, the presence of biochemical hyperthyroidism with 2 of the following was required: diffuse goiter, significant titer of thyroid peroxidase or thyroglobulin autoantibodies (a titer of 1:100 was considered significant), or both, and the presence of thyroid ophthalmopathy. Free T4, T4 and TSH were measured by Chemiluminescence method on Immunolite®. Thyroid autoantibodies were measured by a microparticle enzyme immunoassay. Thyroid receptor antibodies were not done because of unavailability of the diagnostic assays. Eye disease was defined according to the presence of eye signs in categories 2-6 of the NO SPECS classification.[9]

Patients were assessed by a staff endocrinologist at 3, 6, 12 and 18 months. The usual policy is to follow the patients till 18 months for disease remission, otherwise the patient is offered other modes of treatment. Patients were prescribed a titration regime of thionamides according to Abraham *et al.*,[5] in which the dose of thionamides was titrated according to the free T4 and TSH. They were also educated about the side effects of the medicine and were asked to get complete blood picture with granulocyte count in case they develop fever or sore-throat or skin rash. At each visit, patients were examined for signs and symptoms of Grave's disease including goitre and eye signs and were asked about any side effects. Patients were categorized into 2 groups; remission group, and treatment failure group. Patients, who were advised to stop treatment after they became euthyroid at 6, 12 and 18 months follow-up, were placed in the remission group, while patients who developed hyperthyroidism after stopping treatment at anytime during the period of eighteen months were termed as relapse and those whose treatment never stopped, were placed in the treatment failure group. The main outcome was the measurement of remission of Grave's disease with oral anti-thyroid medicines.

Patients of hyperthyroidism given radio active iodine or having causes other than Grave's disease and those having malignant opthalmopathy, myopathy, cardiac arrhythmia, heart failure, weight loss > 10%, pregnancy, poor compliance and follow-up of less than 18 months, were excluded.

Statistical tool used for data entry and evaluation was SPSS 13.0. Association between categorical independent variables (gender, palpable goiter, positive anti-thyroid antibodies, eye signs, patients with age less or greater than 40 years) and outcome was measured using chi-square and Fischer's exact test while t-test was used for quantitative independent variables (age, mean free T4, dose of carbimazole). Multivariate analysis was done using logistic regression model to study the effect of multiple variables associated with the remission in Grave's disease. A p-value of less than 0.05 (level of significance) was taken as significant.

RESULTS

In the analysis of 74 patients of Grave's disease, females were predominant (62.6%) with a mean age of 41 years. During the follow-up period of 18 months, 41.9% (n=31: males 12, females 19) of patients went into remission, 44.5% (n=33: males 12, females 21) never went into remission, while 13.6% (n=10: males 4, females 6) went into relapse, thus patients with treatment failure were 58.1% (n=43: males 16, females 27). Remission rate calculated was 41.9%. All patients tolerated the oral anti-thyroid agents well and none of the patients developed any side effects.

Table I and II show the clinical symptoms, remission and relapse rates at different stages of follow-up. Table III highlights different variables and their impact on remission and treatment failure groups. No statistical difference was observed in males and females in remission and treatment failure groups. Univariate analysis showed that the initial free T4 level was significantly different ($p < 0.05$) in patients in remission and treatment failure groups. Multivariate analysis showed only initial free T4 level was found to be a significant predictor of outcome. Positive anti-microsomal antibody patients (n=27) had higher treatment failures (odds ratio: 2.55: 95%, CI 0.69 – 9:31) compared to negative ones, although the difference was not statistically significant ($p = 0.13$) on univariate and multivariate analysis.

Table I: Symptoms in patients with Grave's disease at different stages of follow-up (n=74).

Symptoms	Initial visit	Follow-up			
		3 months	6 months	12 months	18 months
Palpitations	42 (57%)	7 (9.5%)	4 (5.4%)	11 (14.8%)	6 (8.1%)
Fatigue	32 (43.2%)	2 (2.7%)	4 (5.4%)	11 (14.8%)	7 (9.5%)
Sweating	21 (28.3%)	7 (9.5%)	1 (1.3%)	2 (2.7%)	0 (0%)
Weight loss	64 (86.4%)	13 (17.5%)	8 (10.8%)	15 (20.7%)	12 (16.2%)
Heat intolerance	37 (50%)	6 (8.1%)	3 (4.1%)	5 (6.7%)	0 (0%)
Muscle cramps	4 (5.4%)	3 (4.1%)	2 (2.7%)	5 (6.7%)	1 (1.3%)
Tachycardia	43 (58%)	11 (14.8%)	9 (12.1%)	8 (10.8%)	7 (9.5%)
Warm moist skin	9 (12.1%)	5 (6.7%)	2 (2.7%)	2 (2.7%)	3 (4.1%)

Table II: Remission and relapse rates at different stages of the follow-up.

Group	Follow-up*			
	3 months	6 months	12 months	18 months
Patients in remission	0%	9 (12.2%)	22 (29.7%)	31 (41.9%)
Patients with replase	-	-	3 (4.1%)	7 (9.5%)

** Percentages calculated from the total patients (n=74). At the end of 18 months, 41.9% of patients were in remission, 9.5% relapsed making a total of 58.1% (n=43) patients with treatment failure.*

Table III: Impact of different variables on remission and medical treatment failure groups.

Variables	Remission group	Treatment failure group	Odds ratio	p-value
Number of patients	31 (41.9%)	43 (58.1%)	-	-
Gender				
Males	12 (42.8%)	16 (57.14%)	1.06 (0.41-2.75: 95% CI)	0.543
Females	19 (41.3%)	27 (58.6%)		
Age				
Mean	43 years	42 years	-	0.698
Median	44 years	40 years		
Mode	30 years	40 years		
SD	12.0	15.2		
Outcome in patients < 40 years of age (30/74 or 40%)	11 (35.4%)	19 (44.1%)	0.69 (0.26-1.79: 95% CI)	0.305
Outcome in patients ≥ 40 years (43/74 or 58%)	20 (64.5%)	24 (55.8%)		
Mean free T4 on first visit	2.3 ng/dl	4.7 ng/dl	-	0.025
Mean dose of Carbimazole	31.6 mg	34.6 mg	-	0.340
Clinically palpable goitre	25 (80%)	35 (81%)	1.05 (0.32-3.40: 95% CI)	0.583
Positive anti-micrososmal antibody	10 (32.5%)	17 (39.5%)	2.55 (0.69-9:31: 95% CI)	0.134
Positive Anti-thyroglobulin antibody	12 (38.7%)	12 (27.9%)	0.58 (0.17-1.99: 95% CI)	0.291
Presence of eye signs	8 (25.8%)	16 (37.2%)	1.76 (0.64-4.89: 95% CI)	0.197

CI = Confidence interval; SD = Standard deviation.

DISCUSSION

The outcome of Graves' disease treatment is variable, and hence, identifying factors that could predict treatment outcome before starting treatment will be helpful for the patients. In our experience, the remission of Graves' disease in adults is not satisfactory, only 41.9% of patients experiencing successful remission after cessation of medical therapy. This continues the general trend for the decreasing likelihood of remission reported in recent years.[10-12] The finding that a high percentage of patients eventually required radioiodine, has later led us to offer radioiodine as an option for first-line therapy.

It is well noted that there was no difference in remission or treatment failure rates in relation to gender, age, anti-microsomal/thyroglobulin antibodies, ophthalmopathy and size of goiter. Several studies reported poor prognosis after medical treatment and the influencing factors on the remission rates include age, gender, duration of symptoms before the start of treatment, dosage of anti-thyroid drugs, goiter size, opthalmopathy, severity of hyperthyroidism and presence of thyroid antibodies.[1,2,13,14] Although this study did not show age as a predictor of treatment remission or failure, some previous studies did mention that younger patients have more treatment failures compared to older patients.[1] The reason behind this finding could be the small sample size and short duration of follow-up in the presently reported patients.

High free T4 on initial presentation is associated with higher treatment failures compared to low free T4 level. This finding is in accordance with the studies from Taiwan, Iran and Saudia.[10,15-17] However, two of the studies mentioned high free and total T3 instead of free T4 as a predictor of treatment failure.[10] Beside high free T4 or T3, these studies also found that presence of large goiter, past history of recurrence, and ophthalmology suggest aggressive disease and the authors concluded that alternate treatment options should be offered to such patients.

Measurement of thyroid antibodies especially anti-microsomal and thyroid receptor antibodies (TRAb) are essential in the diagnosis and prediction of disease remission. Since, TRAb were not assayed in our centre making comparison difficult in our case, we also have not found any association of other thyroid antibodies with disease remission or failure. Several previous studies have explained the important relationship between the high titre of these antibodies and disease relapse.[4-6,8,10,15,17] Unavailability of TRAb at the study centre could be a possible reason for the lack of association of thyroid antibodies with disease remission in this study.

There are a few limitations seen in this study. These include the short follow-up of 18 months and small sample size due to lack of follow-up of some patients.

CONCLUSION

The remission rates with oral anti-thyroid treament are rather high. Patients who do not enter remission during a period of 12-18 months of treatment, those who develop replase, and those who have aggressive disease on the initial presentation should be offered alternate treatments options like radio-iodine ablation or surgery. Physicians who hesitate to use radio-iodine as a first-list therapy would be able to identify reliable predictors of remission or relapse following oral anti-thyroid medication.

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